SEVERAL SYNTHETIC APPLICATIONS OF O-STANNYL KETYLS

By

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To Mom and Dad,

with all my love, respect, and gratitude

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I can still remember my first day of kindergarten. I recall how scared I was as I watched my mom drive away leaving me in a strange and unusual place. I would never have dreamed that after almost 22 years and countless teachers, I would still be in school. Before I can begin to recognize those who helped me in my higher education, I feel I should express my gratitude to my parents and all of the teachers who guided me through my early years. Now that I have reached the pinnacle of my education, there are many people whom I should acknowledge for their guidance, understanding, and friendship.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

SEVERAL SYNTHETIC APPLICATIONS OF O-STANNYL KETYLS

By

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Chairman: Eric J. Enholm
Major Department: Chemistry

This dissertation investigated the free-radical-induced formation of O-stannyl ketyls. These reactive species were generated by reaction of tin hydrides or allyltin reagents with ketones under standard free radical conditions. The goal of this study was to utilize O-stannyl ketyls as synthetically useful intermediates. Thus, new methodology was developed which demonstrates the various reactions which these species undergo and promote. Moreover, the methods discussed herein offer the synthetic chemist a chemically neutral alternative to established ionic methods, which frequently produce problems due to their inherent acidic or basic reaction media.

The first area of study was the O-stannyl ketyl-promoted cyclopropane ring fragmentation of α-ketocyclopropanes. The

applications of the resulting distonic enolate radical intermediate were examined. The radical reacted with a tethered olefin to produce bicyclic compounds.

The second area of study examined the reaction of tributyltin hydride with enones. The method produced a tin(IV) enolate by a neutral free radical approach. The enolate was quenched with several electrophiles to afford aldol, alkylation, and conjugate addition products.

The third area of study further utilized the ketyl's ability to induce the formation of new carbon-carbon bonds. An allyl stannane bearing an electron-withdrawing ester moiety was prepared which reacted with enones under free radical conditions to introduce a new carbon bond at the β-site of the enone.

The fourth and final area of study introduced a free radical approach to asymmetric ketone reduction via the O-stannyl ketyl intermediate. Several chiral tin hydride reagents were prepared, and their asymmetric reductive capacity was examined.

CHAPTER 1
INTRODUCTION

When a covalent bond is homolytically cleaved, a reactive intermediate known as a free radical is produced. This species is chemically neutral while possessing an unshared electron.[1] Like carbocations, most carbon-centered radicals are sp^2 hybridized and planar, however, the *p* orbital perpendicular to the plane of the bonding orbitals of the radical species is not empty; it contains the odd electron.[2] The reactivity which radicals exhibit is determined by the atom bearing the radical and its substituents.[3]

It is widely recognized that the first studies of radical chemistry were in 1900, when Gomberg researched the formation and reactions of the triphenylmethyl radical.[4] Synthetic applications of radicals were realized in 1937 when Hey and Waters discovered the phenylation of aromatic compounds by benzoyl peroxide, and Kharasch proposed that the anti-Markovnikov addition of hydrogen bromide to an alkene was a radical chain process.[5,6] Synthetic radical chemistry evolved slowly over the following thirty to forty years where it was mainly applied to copolymerization reactions.[1,7]

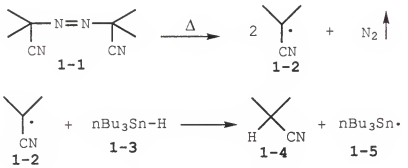
Significant changes occurred in the middle 1970s when new synthetic methods utilizing radicals, particularly in the

area of aromatic substitution reactions, were discovered.[8] Within the last 20 years, the use of radicals in organic synthesis has increased dramatically. The use of alkyl radicals in the formation of aliphatic carbon-carbon bonds (the backbone of organic compounds) has proven to be an extremely valuable method in the synthesis of many target molecules.[1,9]

There are well-defined advantages of using free radicals over ions in organic synthesis. Obviously, radicals are a different form of reactive species, and thereby exhibit different chemoselectivity, regioselectivity, and stereoselectivity (discussed later). In addition to these inherent differences, there are a few more direct benefits in using radical methodology. Solvation effects, although they do exist, are less significant in neutral free radical reactions. Consequently, radicals are more effective in reactions involving large steric interactions or molecules which contain many polar carbon-heteroatom bonds.[3] Racemization at adjacent or remote chiral centers is not as problematic in radical processes. Unlike many anionic methods, most radical reactions are carried out in the absence of acid or base.[1] In addition, the inherent basicity of nucleophilic carbanions can epimerize sensitive centers, such as those adjacent to a carbonyl group.[3] Since the radical species, as well as the typical radical reaction medium is neutral, protecting groups are not necessary to preserve the functionality of chemically sensitive groups.

As free radical chemistry continues to grow, it seems that a species once thought to be uncontrollable, indiscriminate, and highly reactive has become domesticated and extremely useful.[3]

In studying free radical reactions it is first necessary to understand the basic principles. Radical processes are typically chain reactions. The first step, initiation, is the preliminary step where the reactive intermediate radical is first formed. Heat as well as light can promote initiation. There are numerous radical initiators that are commercially available. Some of these include: t-butyl perbenzoate, dibenzoyl peroxide, di-t-butyl peroxide, and di-t-butyl peroxalate. The most commonly used initiator is azobisisobutyronitrile (AIBN), since some of the peroxide initiators can explode without warning. AIBN (**1-1**), which



Scheme 1-1

has a half-life of *ca.* 2 h at 80°C, thermally decomposes to lose nitrogen gas and afford two cyanoisopropyl radicals **1-2** (Scheme 1-1). These radicals are quite unreactive, although capable of abstracting a hydrogen atom from the weak

tributyltin hydride (**1-3**) Sn-H bond (bond dissociation energy of 73.7 kcal/mol) to provide the tributyltin radical **1-5** and 2-methylpropanenitrile (**1-4**).[3]

Tributyltin hydride (TBTH) has been known to participate in free radical reactions for more than thirty years.[10] This dissertation will not attempt to cover the vast amount of chemistry in which TBTH participates; however, there are some very good reviews available.[1,9,11] The AIBN/TBTH combination constitutes the majority of current radical reactions including the work discussed in this dissertation.[9c]

The concentration of radicals at any given time in the chain reaction is limited by the slow rate of initiation.[3] This phenomenon, combined with careful control of substrate to initiator ratio, minimizes the radical-radical reactions which terminate the chain. The chain reaction develops in the next step termed progagation. There are five types of propagation steps, all of which lead to new radicals.[1] These are shown in Scheme 1-2 and consist of: substitution (abstraction) reactions (eq. 1), addition reactions (eq. 2), elimination (fragmentation) reactions (eq. 3), rearrangement reactions (eq. 4), and electron transfer reactions (eq. 5a and b). A brief discussion of the first four is necessary for the purposes of this dissertation.

The substitution (abstraction) reaction (eq. 1) is one of the more commonly used radical reactions in organic

$$R\cdot + AB \longrightarrow RA + B\cdot \qquad \text{(eq.1)}$$

$$R\cdot + AB \longrightarrow RAB\cdot \qquad \text{(eq.2)}$$

$$RAB\cdot \longrightarrow RA + B\cdot \qquad \text{(eq.3)}$$

$$RAB\cdot \longrightarrow ARB\cdot \qquad \text{(eq.4)}$$

$$R^- + M^{n+} \longrightarrow R\cdot + M^{(n-1)+} \qquad \text{(eq.5a)}$$

$$RX^{\cdot-} + RY \longrightarrow RX + RY^{\cdot-} \qquad \text{(eq.5b)}$$

Scheme 1-2

synthesis. Halide abstraction was discovered in 1957.[12] As shown in Scheme 1-3, atom abstraction involves the reaction of tin radical **1-5** with compound **1-6** to generate compound **1-7** and an organic radical **1-8**. The newly formed radical can

$$\underset{\textbf{1-5}}{Bu_3Sn\cdot} + \underset{\textbf{1-6}}{RX} \longrightarrow \underset{\textbf{1-7}}{Bu_3SnX} + \underset{\textbf{1-8}}{R\cdot}$$

$$\underset{\textbf{1-8}}{R\cdot} + \underset{\textbf{1-3}}{Bu_3SnH} \longrightarrow \underset{\textbf{1-9}}{R\text{-}H} + \underset{\textbf{1-5}}{Bu_3Sn\cdot}$$

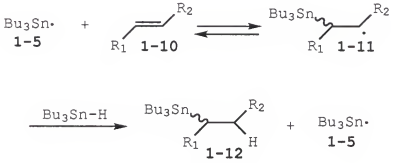
X = halogen, -SR', -SeR', $-NO_2$

Scheme 1-3

then abstract a hydrogen atom from TBTH (**1-3**) to afford the reduced product **1-9** and regenerate **1-5** which continues the chain.

The reactivity of the halides is predominately governed by the nature of the halogen according to the sequence RI>RBr>RCl>>>RF. Bromides and iodides react smoothly, but chlorides tend to be sluggish.[11] Even though fluorides are usually unreactive, there are a few reported instances of fluorine abstraction being used in synthesis.[13] The nature of the organic group also influences the reaction since free radicals are involved as intermediates. The reactivity trend follows the stability of the radicals: tertiary > secondary > primary. It should be noted that thiols, thioethers, selenides, and nitro groups can also be reduced using this method.[11]

A carbon-centered radical can also be generated by addition reactions of tin radical to multiple bonds. As seen in Scheme 1-4, tributyltin radical **1-5** can add reversibly to alkene **1-10** to form the intermediate radical species **1-11**.



Scheme 1-4

Upon hydrogen atom abstraction from another molecule of TBTH, hydrostannylated product **1-12** and tributyltin radical **1-5**

are produced. The criterion for a radical chain process has been satisfied since another molecule of tributyltin radical is generated, which can continue the chain reaction.

So far, this dissertation has focused on reductive free radical chain reactions, and how they can produce carbon-centered radicals, followed by hydrogen atom abstraction. From a synthetic standpoint, applications of free radicals in the formation of carbon-carbon bonds are more significant and useful. Before one can successfully use radicals in synthesis, one must understand the basic physical organic principles which dictate how and why these species react with various functionalities.

Generally speaking, there are two simple rules that can very often be applied to radical chain reactions. There is the thermodynamic parameter which utilizes the strength of the bonds that are broken and formed as a rough guideline for the rate of the reaction. In addition, there is the kinetic parameter, which utilizes frontier molecular orbital (FMO) theory to help explain the various substituent effects on the reactivity of the radical and the species to which the radical is reacting.[1]

The FMO theory can be applied to radical chemistry to help generalize favorable reaction criteria and unfavorable reaction criteria. When applying this theory in free radical addition reactions (represented by eq. 2 in Scheme 1-2), the orbitals considered are the singly occupied molecular orbital (SOMO) of the radical and the highest occupied molecular

orbital (HOMO) as well as the lowest unoccupied molecular orbital (LUMO) of the multiple bond. The greatest interaction or "overlap" between orbitals occurs when they are of comparable energy. Any phenomena which leads to lowering the energy gap between the interacting orbitals tends to lower the activation energy of the reaction.

There are several electronic characteristics which determine the relative energy of the orbitals, thereby determining the nature of the reacting species. An electron-deficient (electrophilic) radical, usually possessing an electron-withdrawing substituent, has a low-energy SOMO. An electron-rich (nucleophilic) radical, usually possessing an electron-donating substituent, has a high-energy SOMO. An electron-deficient multiple bond, possessing an electron-withdrawing substituent, has a low-energy LUMO. An electron-rich multiple bond, possessing an electron-donating substituent, has a high-energy HOMO.[14]

For a radical reaction to occur, a favorable SOMO-HOMO or SOMO-LUMO interaction must exist. FMO theory is frequently useful in discerning the orbital of the multiple bond (the HOMO or the LUMO) which has the major interaction with the reacting radical (the SOMO). As seen in Figure 1-1, an electrophilic radical (low SOMO) usually has a greater interaction with the HOMO than with the LUMO. In contrast, a nucleophilic radical (high SOMO) usually has a greater interaction with the LUMO than with the HOMO.[14] Using these

general trends aids in designing successful radical addition reactions.

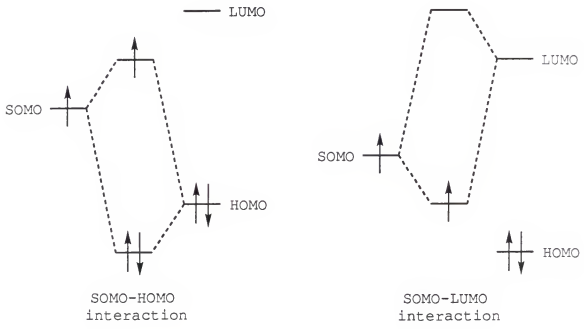
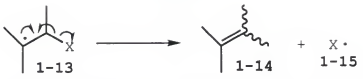


Figure 1-1
The orbital interactions between a radical (SOMO) and a multiple bond (HOMO and LUMO)

In addition to substitution and addition reactions, radicals can also trigger elimination (fragmentation) reactions (eq. 3 in Scheme 1-2). In these reactions, two molecules are formed from one by the homolytic cleavage of a radical's β-bond.[3] As seen in Scheme 1-5, radical **1-13** can undergo β-elimination to yield alkene **1-14** and radical **1-15**. The identity of X is important since only weak C-X bonds undergo β-elimination reactions fast enough to be synthetically useful.[1]

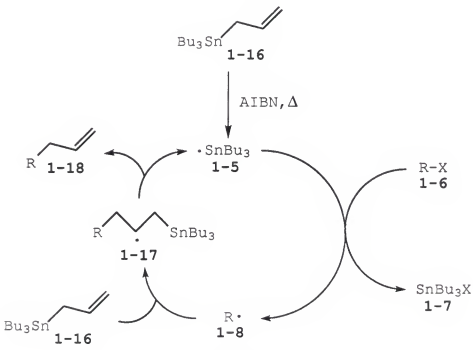
The elimination reaction has become synthetically useful in reactions involving the elimination of trialkyltin



X = halogen, SnR_3, SR, SO_2R, SeR, NO_2, OCSSMe

Scheme 1-5

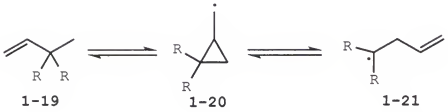
radicals. Keck has used allyltributytin in his allylation reactions which involve a β-elimination to regenerate tributlytin radical.[15] In Scheme 1-6, allyltributyltin (**1-16**), under standard free radical conditions, forms tributyltin radical **1-5** which begins the chain process. Upon abstracting the X atom from a suitable compound **1-6** such as



Scheme 1-6

an alkyl halide, thioether, selenide, or xanthate, free radical **1-8** and tributyltin-X **1-7** are formed. The radical adds to another molecule of allyltin **1-16**, and intermediate addition product **1-17** is then realized. The C-Sn bond β to the radical carbon rapidly fragments yielding allylated product **1-18** and the regenerated tin radical **1-5**, which continues the chain radical process.

The last type of free radical reaction discussed in this section is the rearrangement reaction (eq. 4 in Scheme 1-2). There are only a few radical rearrangements that are fast enough to be useful in syntheses.[1] One example is the vinyl migration which occurs in primary radical **1-19** when it forms the more stable tertiary radical **1-21** (Scheme 1-7). This process is actually a combination of an intramolecular addition (cyclization) of **1-19** to cyclopropylcarbinyl radical **1-20** and an elimination reaction of **1-20** to **1-21**. The

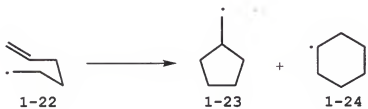


1-19 **1-20** **1-21**

Scheme 1-7

elimination which cleaves the β-C-C bond of **1-20** occurs rapidly due to the release of ring-strain present in cyclopropane rings (28.3 kcal/mol).[1,2]

Often, free radical reactions show different regioselectivities than ionic reactions. When reacting with α,β-unsaturated aldehydes, ketones, and esters, anionic species can react either in a 1,4 or 1,2 addition. In contrast, radicals solely react with the olefinic carbon in a 1,4 addition. The regioselectivity of radical cyclizations is remarkably different from cationic cyclizations. Whereas 1-hexenyl cations tend to cyclize to yield six-membered rings, 1-hexenyl radical **1-22** predominately cyclizes to afford five-membered ring **1-23** instead of cyclohexane radical **1-24** as shown in Scheme 1-8.[1] This phenomenon can be explained by a closer examination of the two cyclization



Scheme 1-8

mechanisms. Cations attack the electron-rich center of the double bond.[1] In contrast, radical additions are generally thought to proceed via an unsymmetrical transition state in which one of the alkene's carbon atoms is closer to the attacking radical.[3] According to Beckwith, an unsymmetrical transition state leads to faster cyclization, forming a five-membered instead of a six-membered ring, because of ring

strain effects.[16] The resulting predominance of 5-exo product formation is also supported by Baldwin's rules, since reactions proceeding under kinetic control occur exclusively in the exo mode.[3,17]

Beckwith has studied the stereochemical implications of 5-hexenyl radical cyclizations in great depth.[16,18] From his results, he was able to formulate a useful model which is based on the relatively strain-free chair-like transition state shown in Figure 1-2. The major products in a 5-hexenyl radical cyclization will be formed from the conformer with

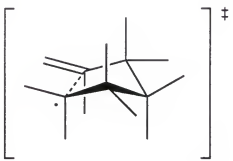
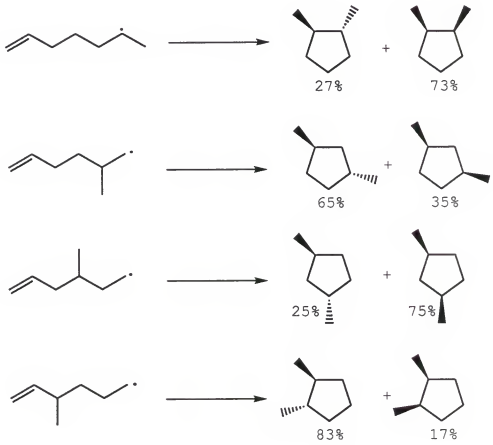


Figure 1-2
Beckwith's chair-like transition state

substituents in the equatorial positions.

It should be stated that more recently, the contribution of the boat conformation has been realized by Houk and Spellmeyer.[19] The boat transition state has been calculated to be only about 1 kcal/mol higher in energy than the chair transition state.[20] Thus, it should be recognized that the Beckwith chair model should not be used as the absolute transition state, but only as a pneumonic device which can

predict the relative stereochemical consequences regardless of the type of transition state occuring. Several examples of these diastereoselective preferences are represented in Scheme 1-9.[3]

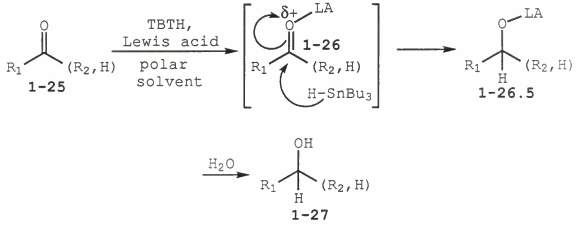


Scheme 1-9

It is important to note that only the relative stereochemical implications of radical reactions have been discussed in the preceding paragraphs. Enantioselective free radical reactions are far less understood, but in the past 6-8 years, asymmetric nonracemic radical chemistry has been

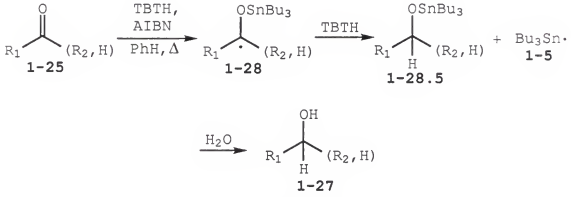
realized and studied. This will be discussed in the introduction section of Chapter 5.

Most of the chemistry in this thesis involves tin-hydride reagents reacting with carbonyls. There are two mechanistic pathways (ionic and free radical) in which hydrostannylation can occur with ketones and aldehydes.[11] The desired pathway strongly depends on the reaction conditions. When a Lewis acid catalyst and polar solvent are employed, the ionic pathway dominates where TBTH acts as a true hydride donor. This is similar to the reductive mechanism of the commonly used sodium borohydride and lithium aluminum hydride reagents. Specifically, the Lewis acid coordinates to the carbonyl oxygen in **1-25** providing intermediate **1-26** (Scheme 1-10). TBTH then donates a hydride to the activated species to afford alkoxide **1-26.5** which can be hydrolyzed to alcohol **1-27**.



Scheme 1-10

The other mechanistic pathway is free radical in approach, which is more applicable to the chemistry described in this dissertation. Under standard free radical conditions, which normally include the use of nonpolar solvents, the tributyltin radical adds at the oxygen of carbonyl **1-25** to produce a carbon-centered radical intermediate **1-28** called an O-stannyl ketyl (Scheme 1-11). The radical then abstracts a hydrogen atom from another molecule of TBTH to afford tin alkoxide **1-28.5** and the regenerated radical **1-5**.[11] The tin alkoxide can be hydrolyzed in workup to yield alcohol **1-27**.



1-25 **1-28** **1-28.5** **1-5** **1-27**

Scheme 1-11

The majority of research in the Enholm group involves O-stannyl ketyls. This species can be considered a pseudo-protected radical anion (Figure 1-3). The O-Sn bond has an expected degree of ionic character, since there is an electronegativity difference between tin and oxygen.

The first studies of tin ketyls utilized the carbon-centered radical to trigger small ring fragmentation, such as

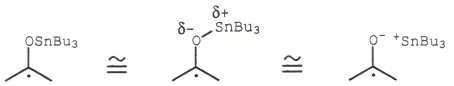
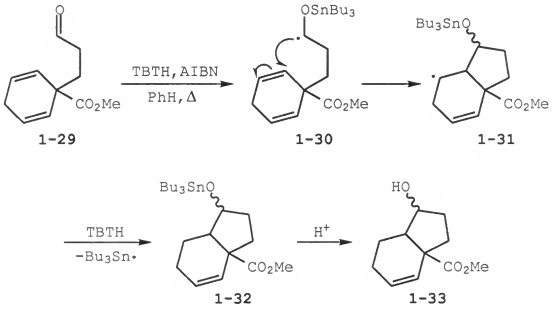


Figure 1-3
The O-stannyl ketyl species

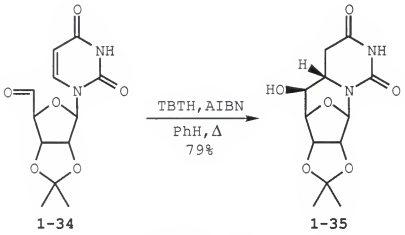
the opening of α-ketocyclopropanes and α-ketoepoxides.[11,21] These studies were primarily mechanistic in approach, but these reactive intermediates were later found to be synthetically useful as well. Tanner performed the first investigations of radically induced ketone reduction using several organotin hydrides.[13b] Beckwith and Roberts showed that tin ketyls can be used to assemble bi- and tricyclic systems.[22] Under radical conditions, ketone **1-29** formed ketyl **1-30**, which cyclized to afford radical intermediate



Scheme 1-12

1-31 (Scheme 1-12). Upon hydrogen atom abstraction from another molecule of TBTH, tin alkoxide **1-32** and the regenerated tributyltin radical were realized. Compound **1-32** was not isolated but simple hydrolysis provides bicyclic alcohol **1-33**. There was no mention of an actual hydrolysis step, but the inherent acidity of a silica gel column was acidic enough to afford alcohol **1-33**. Although the yield was high (90%), Beckwith commented that the reaction was sluggish, requiring excess TBTH and AIBN.

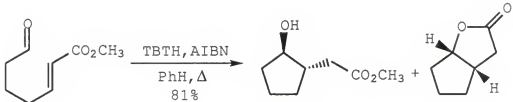
Sugawara and coworkers realized that an activated double bond with an electron-withdrawing substituent would increase the electrophilicity of the double bond, thus reacting more smoothly with the nucleophilic tin ketyl.[23] This is consistent with the generalizations made by the FMO theory discussed previously. Specifically, the ketyl formed from aldehyde **1-34** cyclizes on the activated olefin of the uridine ring system to yield tricyclic compound **1-35** (Scheme 1-13).



1-34 **1-35**

Scheme 1-13

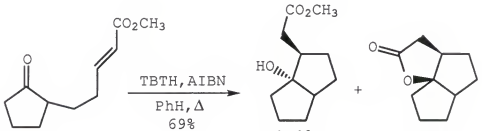
In 1989, the Enholm group began its endeavors in the synthetic use of tin ketyls, when Enholm and Prasad demonstrated that ketones and aldehydes cyclize with activated olefin tethers.[24] They found that aldehyde **1-36** readily cyclized under radical conditions to afford a mixture



1-36 **1-37** : **1-38**
58 : 42

Scheme 1-14

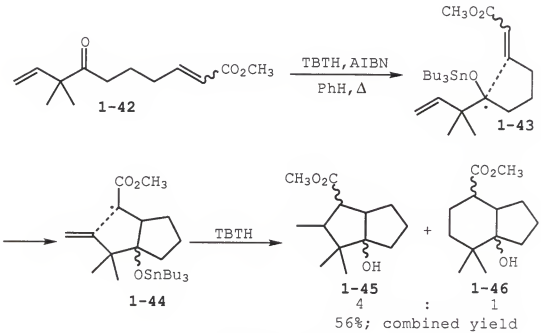
of anti/syn products **1-37** and **1-38** respectively (Scheme 1-14). Using identical synthetic methodology, cyclic ketone **1-39** cyclized to afford products **1-40** and **1-41** (Scheme 1-15). It was found that the electron-withdrawing substituent had a dramatic effect on the cyclizations. Although the unactivated compounds did cyclize, the yields were low.



1-39 **1-40** + **1-41**
76 : 24

Scheme 1-15

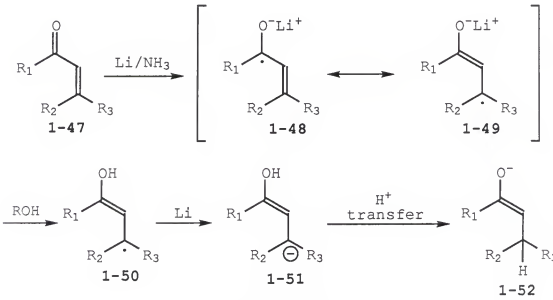
Enholm was also able to apply this methodology in tandem radical cyclizations.[25] Specifically, acyclic ketone **1-42** reacted with TBTH to produce intermediate O-stannyl ketyl **1-43**. The nucleophilic ketyl then cyclized on the tethered electron-deficient olefin producing **1-44** (Scheme 1-16). The resulting electrophilic radical in **1-44** now added to the electron-rich olefinic appendage, which after hydrogen atom



Scheme 1-16

abstraction from TBTH, afforded bicyclic compounds **1-45** and **1-46**. The electronic factors required for favorable additions were carefully arranged in this reaction. It is also worth noting the preference for the formation of the 5-exo product over the 6-endo product in the second cyclization. This is consistent with the arguments that have been previously described.

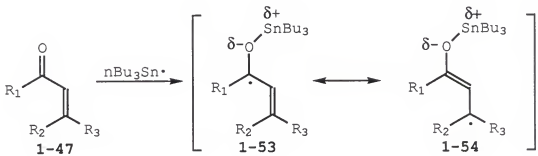
In the previous pages, we have discussed the formation of ketyls from ketones and aldehydes. It is important to recognize that ketyls can be formed from enones and enals as well. The most common reactions of this type involve dissolving metal reductions. Enone **1-47** is reacted with excess sodium or lithium metal in liquid ammonia and one equivalent of a proton donor such as ethanol or *t*-butanol (Scheme 1-17). The resulting resonance stabilized radical anion species **1-48** ↔ **1-49** is protonated to provide allylic radical **1-50**. Upon further reduction by lithium metal to anion **1-51**, proton transfer, which presumably involves either ammonia or a second molecule of **1-51**, occurs to produce enolate anion **1-52**.[26] The frequently encountered problems with this methodology stem from the relatively harsh reaction conditions where other functional groups can be reduced as well as the enone. Moreover, many compounds are not soluble



Scheme 1-17

in Li/NH_3 media, precluding its use in many situations.

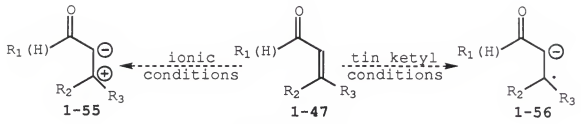
In the last six years, the Enholm group has developed a chemically neutral alternative to metal enolate formation of α,β-unsaturated ketones and aldehydes.[27-31] Ketone **1-47** can be reacted with TBTH under radical conditions to give allylic O-stannyl ketyl **1-53** ↔ **1-54** (Scheme 1-18). Intermediate **1-54** is extremely important in the work that will be presented



Scheme 1-18

in this thesis. It possesses two reactive centers, a radical moiety as well as an enolate moiety. Both reactive sites can be useful to the synthetic chemist. The major challenge is to utilize both reactive centers to form two carbon-carbon bonds in one reaction.

It is significant to note that resonance predicts the classic reactive nature of enones and enals. An electrophilic center is at the β-position, and a nucleophilic center is at the α-position (**1-55** in Scheme 1-19).[32] One example of this ionic methodology utilizes nucleophilic attack at the enone's electropositive β-position with R_2CuLi. The



Scheme 1-19

resulting negative α-carbon can now be trapped with an electrophile such as RBr.

When TBTH is reacted with enones under radical conditions, the electronic nature of the species generated is divergent from the ionic **1-55**. The one-electron induced tin ketyl conditions alter the unsaturated carbonyls inherent reactivity by placing a radical at the β-position and a negative center at the α-position (**1-56** in Scheme 1-19).

This dissertation discusses several synthetic applications of O-stannyl ketyls. The overall goal of this research was not in total synthesis but in new synthetic methodologies which demonstrate various reactions which tin ketyls induce. These reactions included: triggered ring opening, addition to a double bond, induction of enolate and β-radical formation from enones, and abstraction of a hydride from a chiral hydride source.

Chapter 2 examines the O-stannyl ketyl-promoted cyclopropane ring fragmentation of α-ketocyclopropane compounds. The process produces a distonic enolate radical species. The radical reacts with a tethered olefin to form a bicyclic compound.

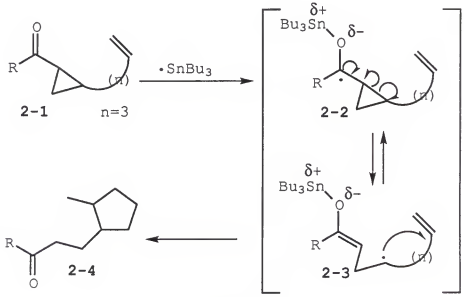
Chapter 3 illustrates how TBTH reacts with α,β-unsaturated ketones to provide allylic O-stannyl ketyls. The tin(IV) enolate, formed after hydrogen atom abstraction, reacts with several electrophiles such as aldehydes, alkyl halides, and unsaturated carbonyls. This provides a mild regioselective alternative to enolate formation which usually requires strong bases or strongly dissolving metal conditions to achieve success.

Chapter 4 examines reactions of 2-substituted allylstannanes with α,β-unsaturated ketones. The prepared tin reagent not only induces allylic O-stannyl ketyl formation, but also forms a new carbon-carbon bond at the β-radical site.

Chapter 5 studies a new facet of the field of enantioselective reductions. Tin ketyls play a role as the intermediate formed before asymmetric hydride abstraction. Several chiral tin hydrides reduce acetophenone to (S)-1-phenylethanol, however, the enantiomeric excesses are low.

CHAPTER 2
O-STANNYL KETYL PROMOTED RING SCISSION REACTIONS OF α-KETOCYCLOPROPANES

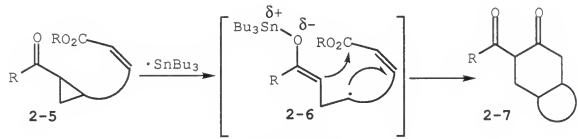
As discussed in chapter 1, when a strained ring such as a cyclopropane is adjacent to a carbon radical, rapid ring opening can occur due to strain release.[1] Similarly, the ketyl formed from the reaction of tributyltin hydride with α-ketocyclopropanes has also been proven to facilitate ring opening, however, this early work was primarily mechanistic in its approach.[21] We wanted to extend this area by using α-ketocyclopropane ketyls as synthetically useful carbon skeletons. As seen in Scheme 2-1, when an α-ketocyclopropane



Scheme 2-1

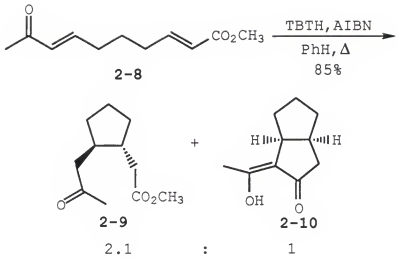
2-1 reacts with tributyltin radical, the resulting ketyl **2-2** can open the ring to form a distonic enolate radical **2-3**. Separated from its anionic component by a methylene unit, the carbon radical can behave like any carbon radical, such as addition to a double bond to afford compound **2-4**. This can be termed a one-electron ($1e^-$) or radical cyclization.

There exists another reactive nucleophilic center due to the presence of the enolate. If an electrophilic center, such as an ester, was present adjacent to the double bond as in compound **2-5**, it might additionally react with the enolate in a Claisen-type reaction via intermediate **2-6** to yield **2-7** (Scheme 2-2). This can be termed a tandem $1e^-/2e^-$ cyclization. Thus, the goal of this project was to generate and utilize both the enolate and the radical species in one reaction.



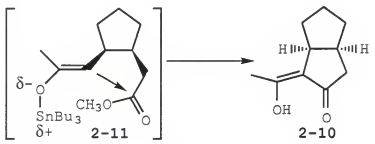
Scheme 2-2

A reaction which could be used as a precedent for a tandem $1e^-/2e^-$ cyclization is shown in Scheme 2-3.[27] When compound **2-8** is reacted with TBTH under standard free radical conditions, the major product **2-9** arises from an



Scheme 2-3

intramolecular $1e^-$ cyclization between the β-carbon radical and the double bond of the unsaturated ester. (A more complete discussion of reactions involving TBTH and α,β-unsaturated ketones will be given in Chapter 3). Notice that the two substituents on the cyclopentane product **2-9** are trans. The minor product **2-10** is cis-fused and significantly different in structure. One rationale for its formation is that an additional Claisen-type two-electron ($2e^-$)

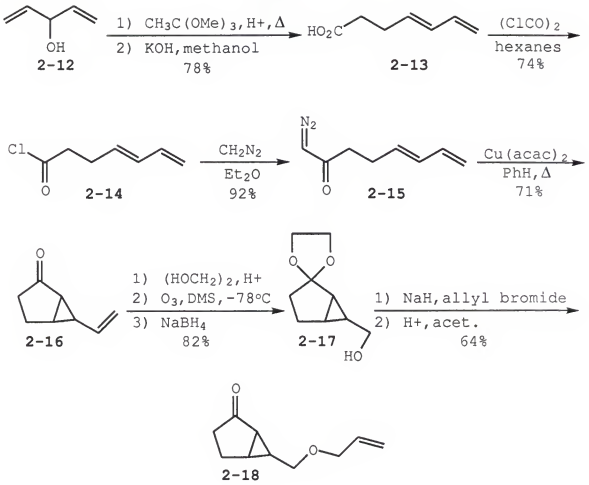


Scheme 2-4

cyclization between the tin enolate and the ester in intermediate **2-11** could have occurred yielding **2-10** (Scheme 2-4). This cyclization can only occur if the substituents are cis, placing the ester much closer in proximity to the enolate versus the trans-form.

We hoped to apply this strategy to α-ketocyclopropanes. Consequently, this would demonstrate the synthetic utility of both the enolate and the distonic radical formed in one reaction from scission of an α-ketocyclopropane. Most of the work herein focuses on $1e^-$ cyclizations as in Scheme 2-1, but a tandem $1e^-/2e^-$ reaction was one of the original goals of this work (Scheme 2-2).

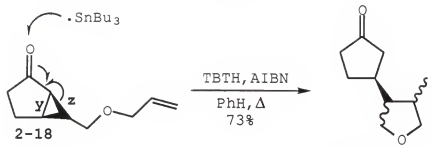
Before our proposed methodology could be studied, the necessary precursors had to be made available. Thus, we began our studies with the synthesis of α-ketocyclopropanes. Our first approach for preparing molecules of this type is shown in Scheme 2-5. Reacting 1,4-pentadien-3-ol (**2-12**) with triethylorthoacetate (ortho-Claisen rearrangement) yielded heptadienoic ester which was subsequently hydrolyzed to the acid **2-13**. Reaction with oxallyl chloride yielded the acid chloride **2-14** which could be converted to diazo ketone **2-15** upon treatment with diazomethane. Vinylcyclopropane **2-16** was generated by refluxing a dilute solution of **2-15** in benzene containing 10 mol% of $Cu(acac)_2$.[33] After ketal protection, ozonolysis of the double bond, and immediate reduction of the resulting aldehyde functionality, alcohol **2-17** was realized. Ketone **2-18** was synthesized by Williamson ether synthesis of



Scheme 2-5

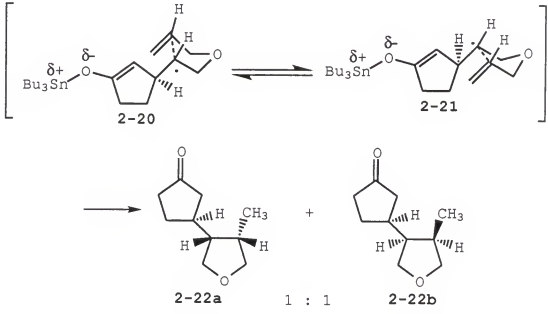
alcohol **2-17** with allyl bromide followed by ketal deprotection with a catalytic amount of *p*-toluenesulfonic acid.

This put us at a juncture to model the $1e^-$ (radical) cyclization (Scheme 2-6a). Upon treatment with tributyltin hydride, compound **2-18** cyclized to form **2-19a** and **b** (1:1 mixture of two diastereomers) in 73% yield. Although conclusive evidence was not obtained, the hydrogens were likely cis on the tetrahydrofuran ring in both products.



Scheme 2-6a

This was predicted by the Beckwith chair model for 5-hexenyl radical cyclizations represented by intermediates **2-20** and **2-21** (Scheme 2-6b).[1,3] The radical centered species leads to two products **2-22a** and **b** via either chair conformer.



Scheme 2-6b

It is also worth noting that although either bond **y** or bond **z** could be cleaved by the ketyl, only bond **z** cleavage

was observed. We believed this result was due to bond **z** having better overlap with the ketyl *p*-like orbital which contains the odd electron (Figure 2-1). This was consistent with other studies of α-ketocyclopropane cleavages which had been performed in the Enholm group.[34]

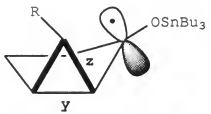
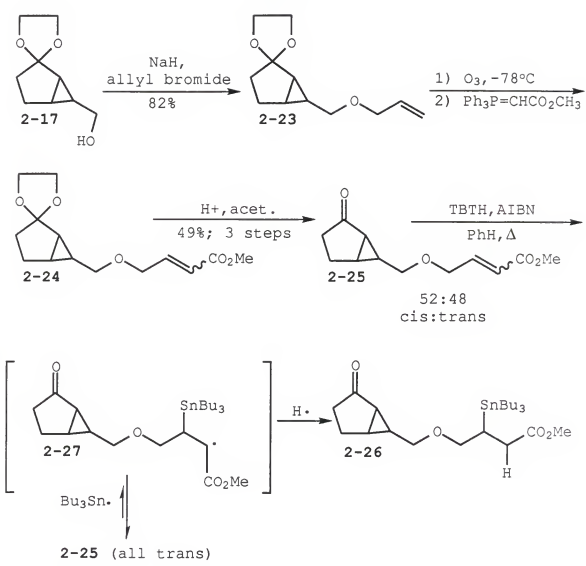


Figure 2-1

Since the $1e^-$ cyclization was successful, we were ready to attempt the tandem $1e^-/2e^-$ cyclization. First, certain alterations to the model structure were performed. As seen in Scheme 2-7, compound **2-17** (previously prepared) was reacted again with allyl bromide in Williamson fashion to yield **2-23**. After cleaving the double bond with ozone, the resulting aldehyde was subjected to a Wittig reaction with methyl(triphenylphosphoranylidene)acetate to form α,β-unsaturated ester **2-24**. Much of the ketal was lost in this step, but fortunately the next step was a ketal deprotection which provided ketone **2-25**. Curiously, the ratio of cis to trans alkenes was nearly 1:1. One would normally expect a greater amount of trans compound in Wittig reactions using a stabilized ylide.[35] Regardless, the compound was ideal to model the tandem $1e^-/2e^-$cyclization.



Scheme 2-7

Upon reaction with tributyltin hydride, the all cis geometric isomer of **2-25** was transformed to the trans compound in 10 minutes (by TLC). After 24 hours and significant amount of starting material depletion (TLC), few distinguishable products were realized. One isolated product appearing pure by TLC had incorporated the tin reagent in its structure such as the proposed compound **2-26**. Although we

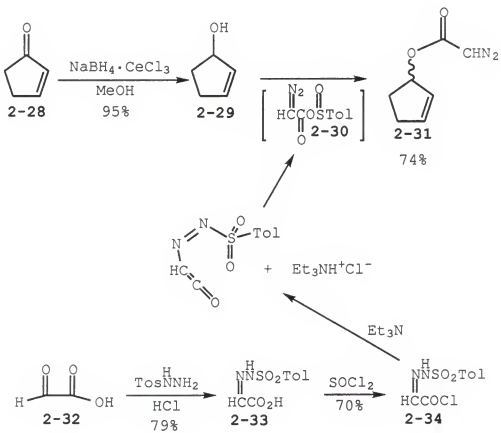
were unable to fully characterize compound **2-26**, its formation is definitely plausible under these reaction conditions. The ^{1}H NMR spectrum revealed strong similarities to the starting ketone **2-25**, except the double bond peaks were not present. The spectrum, although inconclusive, also contained the series of large peaks characteristic of the tin's three butyl groups.

The formation of compound **2-26** was supported by the observance of all the cis starting material rearranging to trans starting material in the first few minutes of the reaction. A reversible hydrostannylation process had ensued via intermediate **2-27**. Although the hydrostannylation would not have hindered the model cyclizations if it had only been a reversible process, it was definitely deleterious in this case due to the tin bonding permanently to the structure after prolonged reaction times.

We speculate that this phenomenon wasn't observed in the previous cyclization (Scheme 2-6a) due to the instability of the radical formed from TBTH adding across the double bond in **2-18**. For hydrostannylated products to be observed, the intermediate radical species must have a lifetime long enough for hydrogen atom abstraction to occur. We believe that hydrostannylation may occur in **2-18**, but it is entirely reversible. The unstabilized electron-rich alkyl radical probably undergoes β-elimination back to starting material faster than a radical which is stabilized by an electron-withdrawing group such as an ester. Thus, the more stable

radical **2-27** might then undergo a competitive reaction with β-elimination, such as hydrogen atom abstraction, to afford hydrostannylated product **2-26**. This would be more likely after prolonged reaction times. Regardless, the desired cyclization did not occur, and it was clear that further structural manipulation was necessary to facilitate the desired cyclizations.

Due to depletion (and cost) of starting materials in the previous synthesis, a shorter, new approach was chosen to continue this work (Scheme 2-8). Cyclopentenone **2-28** was

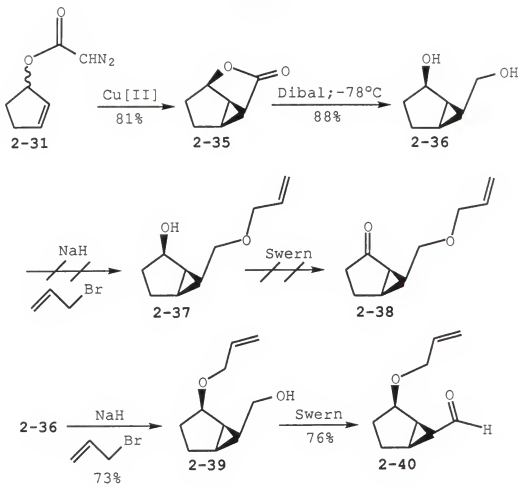


Scheme 2-8

reduced under Luche's conditions to the allylic alcohol **2-29**.[36] Upon reaction with diazo compound **2-30** (prepared *in situ*) diazo ester **2-31** was formed.[37] Compound **2-30** was prepared *in situ* by reacting acid chloride tosyl hydrazone **2-34** with base. To generate **2-34,** an Organic Synthesis preparation was used which reacted glyoxylic acid **2-32** with tosyl hydrazone to yield acid tosyl hydrazone **2-33,** which was converted to acid chloride **2-34** with thionyl chloride.[38]

Diazo ester **2-31** was reacted with a Cu(II) catalyst[39] under refluxing conditions to afford bicyclic lactone **2-35** as shown in Scheme 2-9.[37] After reduction to diol **2-36,** a selective Williamson ether synthesis was attempted using 1.2 equivalents of base and 1.5 equivalents of allyl bromide. Indeed, only one major product was isolable (73%) and was assumed to be alcohol **2-37.** A Swern oxidation would yield **2-38,** identical to compound **2-18** prepared previously in Scheme 2-5. However, the product isolated from the Swern oxidation was aldehyde **2-40,** indicating that in the previous etherification, the secondary alcohol was reacted in preference to the desired primary alcohol. That is, **2-39** had been prepared instead of the desired **2-37.**

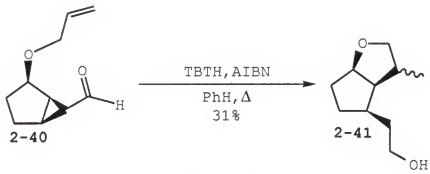
Although frustrated by synthesizing the wrong compound, it was encouraging to notice that essentially the same type of system present in the desired **2-38** existed in **2-40.** That is, a cyclopropane was α to a carbonyl, and a double bond was located 4 atoms away from the cyclopropane. Thus, even though this wasn't the desired product, it fit the generic



Scheme 2-9

scheme for ketyl promoted ring opening and subsequent radical cyclization as portrayed in Scheme 2-1. Therefore, compound **2-40** was reacted with TBTH under radical conditions (Scheme 2-10). The reaction proceeded very slowly, and an additional equivalent of TBTH was necessary to consume all of the starting material. The desired cyclization product **2-41** was isolated in 31% yield. Although the yield was not as high as in the previous $1e^-$ cyclization system (Scheme 2-6), it was promising to discover that our cyclization reaction was

successful with a different substrate. It should be noted that the aldehyde functionality in **2-40** was reduced to the



2-40 **2-41**

Scheme 2-10

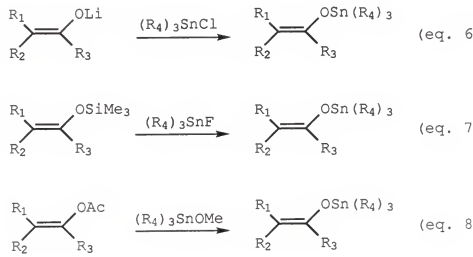
alcohol in **2-41**. This was due to the presence of excess TBTH in the reaction.

It has been shown that α-ketocyclopropane derivatives can be successfully synthesized (*i.e.*, average yield *ca.* 80% for each step). The O-stannyl ketyl can be formed from these derivatives and subsequent ring scission does occur in the bicylo[3.1.0]hexane system. We have utilized the carbon radical formed after scission to cyclize with a tethered double bond. There was also an example of ketyl formation and subsequent radical cyclization of an α-aldocyclopropane. Further studies which utilize the enolate moiety need to be performed.

CHAPTER 3
REACTIONS OF TIN(IV) ENOLATES VIA ALLYLIC O-STANNYL KETYLS

Introduction and Previous Work

Tin (IV) enolates have been widely used in organic synthesis.[40,41] They act as carbon nucleophiles to form carbon-carbon bonds (the backbone of organic synthesis). The tin enolate species is less basic than a lithium enolate but more reactive than a silyl enol ether.[41] As seen in Scheme 3-1, there are a variety of methods of preparing tin enolates. The first method shown (eq. 6) is a transmetallation of a

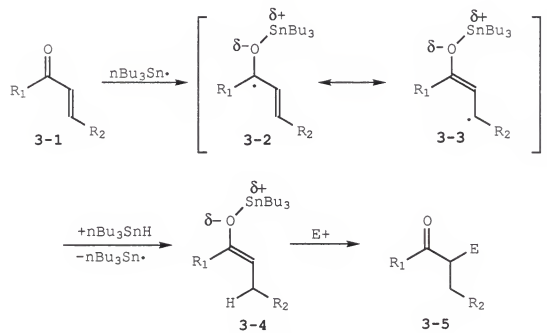


Scheme 3-1

lithium enolate precursor with a trialkyltin chloride.[42] This method is probably the most widely used. Another method is

via a silyl enol ether and trialkyltin fluoride (eq. 7).[43] In addition, tin enolates can be formed by transesterification of an enol acetate (eq. 8).[44] These processes are somewhat inelegant in that they require an additional step(s) to provide the desired intermediate, and strong bases are often used.

As mentioned in Chapter 1, there is a neutral and mild way to form tin enolates. Under standard free radical conditions, tributyltin hydride reacts with an α,β-unsaturated ketone **3-1** to afford an intermediate resonance-stabilized allylic O-stannyl ketyl **3-2** ↔ **3-3** (Scheme 3-2). After

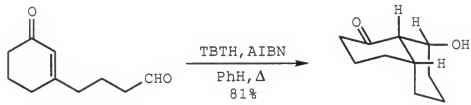


Scheme 3-2

hydrogen atom abstraction to the β-position of **3-3**, a tin(IV) enolate **3-4** is produced.[27-31] The focus of this chapter is

to study various synthetic applications of enolate **3-4** by quenching it with different types of electrophiles to form new carbon-carbon bonds as in the generic product **3-5**.

The first successful application of this methodology in the Enholm group was an intramolecular aldol reaction.[28] Specifically, cyclohexenone precursors with aldehyde tethers were synthesized and reacted with TBTH under standard free radical conditions. One example of this reaction is shown in Scheme 3-3 where enone **3-6** cyclized to form aldol product **3-7**. There was some concern about the competition between the



3-6 **3-7**

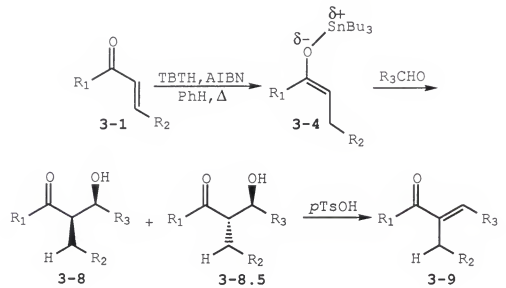
Scheme 3-3

two carbonyl groups reacting with TBTH. However, the more stable allylic O-stannyl ketyl prevailed from the α,β-unsaturated ketone. The enolate provided after hydrogen atom abstraction then cyclized with the aldehyde functionality.

Intermolecular Aldol Reaction

Since an intramolecular aldol reaction was achieved using the methodology we had developed, an intermolecular carbon-carbon bond forming aldol reaction was next attempted.

This bimolecular reaction would better examine the tin enolate's reactivity, since the unimolecular aldol has far less entropic considerations. The reaction sequence followed Scheme 3-4, reacting an enone **3-1** with TBTH to form enolate **3-4**. This enolate could react with an aldehyde to yield a mixture of aldol products, **3-8** (erythro) and **3-8.5** (threo).



Scheme 3-4

The β-hydroxy ketone functionality could now be eliminated under acidic conditions to afford a new unsaturated ketone **3-9**.

The first attempt at an intermolecular reaction was performed in one pot. Specifically, cyclohexenone, cyclohexane-carboxaldehyde, tributyltin hydride, and AIBN were dissolved in benzene, degassed, and refluxed. After consumption of the cyclohexenone, by TLC, the major isolated product was indeed the desired aldol product **3-17** (Table 3-

1). However the yield was only 35%, and several undetermined side products were isolated. Realizing that tributyltin hydride could react with the aldehyde (even though it didn't in the intramolecular examples), generation of the tin enolate *in situ* was attempted with an aldehyde quench. This was first attempted by observing consumption of cyclohexenone by TLC and quenching the presumed tin enolate with the aldehyde at 80°C. The reaction was complete in 1 hr. (isolated yield, 41%). It was at this point where the diastereomeric ratio was examined in more detail. With aldehyde quench at 80°C, the erythro:threo ratio was determined to be 3.8:1. The ratio was determined by NMR integration of the crude reaction mixture. Unfortunately GC was not applicable since the product dramatically decomposed on the column. That is, samples appearing clean by NMR made several GC peaks. A discussion dealing with distinguishing erythro products from threo products will be included later in this section.

The logical progression to improve this diastereomeric ratio is to perform the aldehyde quench at a lower temperature. Limited somewhat by the freezing point of benzene (5.5°C), it was decided to quench the enolate at 10°C. Not only did the erythro:threo ratio improve to 6:1 at this temperature, but also the yield improved to 59%. We now tried the identical reaction in toluene (which could be cooled to -78°C without freezing). After quenching the enolate at -78°C, we were discouraged to find that our

erythro:threo ratio actually decreased to 3:1. At this point it was realized that our optimum reaction conditions were using benzene as solvent, generating the enolate *in situ* , cooling the reaction flask to 10°C, and adding the aldehyde at this temperature. It was with these conditions upon which the project was completed.

The next aldol reaction tried was with the same conjugated ketone, cyclohexenone, but with benzaldehyde as the quench. This was an ideal example since the aldol product, **3-16**, (generated by different means) existed in the literature.[45] Thus, unequivocal proof of structure and stereochemistry by spectral comparison could be made. Using the previous optimum conditions, the products, again a mixture of two diastereomers, were isolated in 73% yield. According to the literature, the threo product contained a benzylic C<u>H</u> doublet of doublet signal at 4.7 ppm with a coupling constant of 3 and 8 Hz. In our results the threo product contained a benzylic C<u>H</u> at 4.9 ppm with a coupling constant of 2 and 8 Hz. The erythro product existed in excess in our results in 6:1 ratio. Its benzylic C<u>H</u> was at 5.4 ppm (an apparent t, J=3 Hz) compared to 5.3 ppm, J=2.4 Hz in the literature.[45] The erythro C<u>H</u>OH peaks were more downfield in the NMR spectrum than threo isomer, whereas in the previous example, 2-(cyclohexylhydroxymethyl)-cyclohexanone,**3-17**, the threo C<u>H</u>OH peaks were more downfield.

The distinguishing factor in the determination between threo isomers is the C<u>H</u>OH coupling constant, whereas the

erythro CHOH is smaller (usually by 2-5 Hz) than the threo CHOH coupling.

Whereas Yamamoto found erythro-selective aldol condensations with triphenyl tin enolates, Stille found mostly threo selectivity with triethyltin, trimethyltin and tributyltin enol stannanes.[46,47] In both cases, the reaction temperature was -78°C. When reacting the cyclohexanone tributyltin enol stannane at 45°C, Stille found that the erythro selectivity was predominant for the aldol reaction with benzaldehyde.[47] He explained the ethryo product's formation using a boat transition state shown in Figure 3-1. He went on to comment on the difference in erythro/threo selectivity with different temperatures (-78°C vs. 45°C) by saying, "the reasons for the predominate formation of the erythro aldols at higher temperatures are not clear."[47]

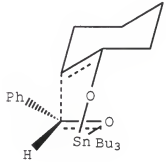


Figure 3-1
Stille's proposed boat transition state

The removal of any excess tributyltin hydride and other possible tin byproducts was facilitated using a Curran method involving treatment with 1,8-diazobicyclo[5.4.0]undec-7-ene

(DBU) and iodine and rapid filtration through silica gel.[48] The method was found to be successful, since most of the tin compounds present after the reaction could be removed prior to flash column chromatography.

Table 3-1
Aldol reaction results

Enone	Ald.	Aldol	Yield (%) (erythro : threo)	Elim. Product	Yield (%) (E : Z)
3-10	**3-13**	$R_{1a}CHOHR_{3a}$ **3-16**	73 (6:1)	$R_{1a}=CH-R_{3a}$ **3-24**	92 (82:1)
3-10	**3-14**	$R_{1a}CHOHR_{3b}$ **3-17**	59 (6:1)	$R_{1a}=CH-R_{3b}$ **3-25**	95 (20:1)
3-10	**3-15**	$R_{1a}CHOHR_{3c}$ **3-18**	56 (4:1)	$R_{1a}=CH-R_{3c}$ **3-26**	89 (13:1)
3-11	**3-13**	$R_{1b}CHOHR_{3a}$ **3-19**	79 (1:1)	$R_{1b}=CH-R_{3a}$ **3-27**	78 (15:1)
3-11	**3-14**	$R_{1b}CHOHR_{3b}$ **3-20**	62 (3:1)	$R_{1b}=CH-R_{3b}$ **3-28**	90 (>100:1)
3-11	**3-15**	$R_{1b}CHOHR_{3c}$ **3-21**	63 (1:1)	$R_{1b}=CH-R_{3c}$ **3-29**	94 (41:1)
3-12	**3-13**	$R_{1c}CHOHR_{3a}$ **3-22**	52 (2.5:1)	$R_{1c}=CH-R_{3a}$ **3-30**	53 (23:1)
3-12	**3-14**	$R_{1c}CHOHR_{3b}$ **3-23**	45 (4:1)	$R_{1c}=CH-R_{3b}$ **3-31**	88 (34:1)

Enones used: 2-cyclohexenone (**3-10**), 2-cyclopentenone (**3-11**), 4-hexen-3-one (**3-12**)

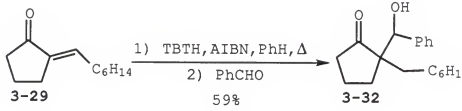
Aldehydes used: benzaldehyde (**3-13**), cyclohexanecarboxaldehyde (**3-14**), heptanal (**3-15**)

R_{1a}= 2-cyclohexanone, R_{1b}= 2-cyclopentanone, R_{1c}= 4-(3-hexanone), R_{3a}= Phenyl, R_{3b}= cyclohexyl, R_{3c}= n-hexyl

The remainder of the tin aldol reactions are shown in Table 3-1. Yields are for combined erythro, threo products.[29,31] Only spectral data for the major erythro product is recorded in the experimental section for the remaining six aldol examples. Yields were highest for the reaction of cyclic unsaturated ketones with benzaldehyde. It follows that the acyclic examples tended to yield more unidentifiable byproducts. The corresponding eliminated products and yields are shown as well. The eliminations proceeded with excellent yields with one exception, the elimination of **3-22** to **3-30**. This was finally accomplished in 53% yield with more byproducts than the rest of the eliminations; a small amount of starting material remained. Additional acid only decreased the yield and increased the amount of byproducts.

Two unsuccessful reactions that are worth noting include the attempted aldol reaction using unsaturated ketones methyl vinyl ketone and trans-chalcone. It was undetermined whether the enol stannane was formed at all in the case of MVK, since before the aldehyde quench was performed, numerous products were observable by TLC. This failure was possible considering the ability of MVK to polymerize under radical conditions. The major product in the chalcone example was one where the olefin had simply been reduced. This is consistent with previous work with this compound in the Enholm group.[49]

Recognizing that elimination products **3-24** - **3-31** are in fact unsaturated ketones enables the possibility that an additional tin aldol reaction might now be performed. Compounds **3-16, 3-19,** and **3-22** (containing a β-phenyl substituent) were not chosen to test this methodology, since trans-chalcone was only reduced under the reaction conditions. The reaction was attempted using compound **3-29** and benzaldehyde as the aldehyde quench to afford **3-32** (Scheme 3-5).



3-29 **3-32**

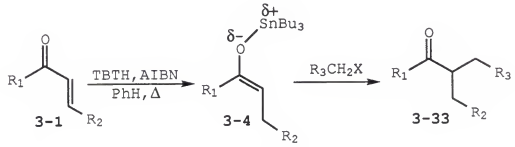
Scheme 3-5

The entire process must be done in 3 pots. That is, the first aldol reaction, the elimination, and the second aldol reaction must be performed in separate reaction flasks. Thus, the first free radical method to introduce two carbon substituents α to a carbonyl has been accomplished.[29,31]

Alkylation Reaction

Due to the success of using TBTH to initiate aldol reactions between enones and aldehydes, it was determined that the method might also be applicable between enones and alkyl halides. This process is expressed in Scheme 3-6.

Enone **3-1** can react with TBTH to form the tin(IV) enolate **3-4** as discussed previously and be quenched with an alkyl halide to afford alkylated product **3-33**. There are two



Scheme 3-6

concepts particularly worth noting in the reaction sequence. First, this radical reaction provides a direct contrast to how an α,β-unsaturated ketone classically undergoes additions in free radical reactions with an alkyl halide.[1,3,9c] The normal attack of the alkyl radical, which forms from the alkyl halide, occurs at the β-position in a 1,4-manner as it does with essentially all one and two electron donors. By simply delaying the addition of the alkyl halide reagent, the tin(IV) enolate forms first, and α-alkylation follows. Greater flexibility is now possible in both types of reactions because similar starting materials are used.

The first attempt at tin mediated alkylation was performed similarly to the intermolecular tin aldol condensation. Specifically cyclohexenone, tributyltin hydride, and AIBN was dissolved in benzene, degassed, and refluxed for four hours. After the starting cyclohexenone

had been consumed and presumably the tin enolate generated, benzyl bromide (4 eq) was added. A reaction was also tried using allyl bromide as the alkyl halide quench. Although a small amount of alkylated product was isolated in both cases, the major product in these reactions was cyclohexanone. This meant that the enolate formed but was predominately quenched with proton sources available in work up. Obviously, the tin(IV) enolate was simply not reactive enough to be alkylated in high yields.

First, we attempted to achieve more alkylation by running the reaction in toluene, and thereby refluxing the reaction pot at 110°C. This proved to be unsuccessful in achieving higher yields. Next, an attempt was made to exchange the metal from tin to lithium to provide a more reactive enolate. Magnesium was also tried. This was performed by adding lithium bromide or magnesium bromide, respectively to the presumed tin enolate that had been generated *in situ*.[50] After quenching these enolates with allyl bromide, no significant improvement in alkylation was observed. Finally, it was decided that hexamethylphosphoramide (HMPA) should be added before the alkyl halide quench.[50] This additive can increase the nucleophilic capacity of the enolate. The high coordination ability of HMPA allows it to act as a Lewis base, thus increasing the polarity of the tin(IV) enolate (Figure 3-2). This was found to improve alkylation yields significantly. When 5 equivalents of HMPA was added prior to the alkyl halide, yields improved by as

much as *ca.* 50%. Experiments were performed to optimize yields with both 2 equivalents and 8 equivalents of HMPA.

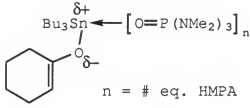


Figure 3-2
Activation of enolates with HMPA

These reactions yielded the alkylated product in better yields than without using HMPA, but not as good as using 5 equivalents. The alkylation results are shown in Table 3-2. As in the aldol results, cyclic enones seemed to facilitate higher yields than acyclic enones.[30,31]

With a better understanding of the alkylation methodology, our attention was next turned toward more sophisticated systems. Specifically , two sugar iodide derivatives **3-49** and **3-50** (Figure 3-3) were considered,

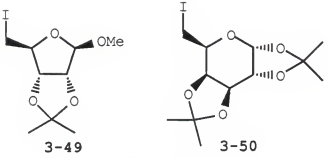
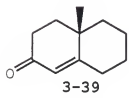
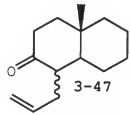
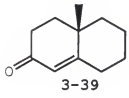
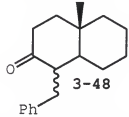


Figure 3-3
Sugar iodide derivatives

Table 3-2
Alkylation results

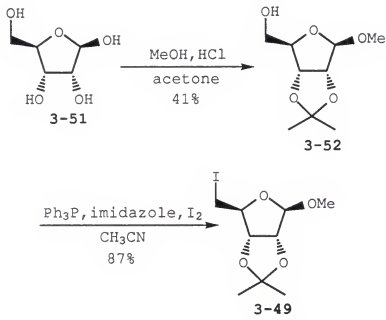
Enone	Halide	Product	Yield (%)
3-10	**3-34**	2-Allylcyclohexanone (**3-40**)	71
3-10	**3-35**	2-Benzylcyclohexanone (**3-41**)	69
3-10	**3-36**	2-Hexylcyclohexanone (**3-42**)	61
3-12	**3-34**	4-Ethylhept-6-en-3-one (**3-43**)	48
3-12	**3-35**	4-Benzyl-3-hexanone (**3-44**)	40
3-12	**3-37**	3-Ethyl-1-phenyl-1,4-hexanedione (**3-45**)	62
3-12	**3-38**	Methyl 3-ethyl-4-oxohexanoate (**3-46**)	80
 **3-39**	**3-34**	 **3-47**	76
 **3-39**	**3-35**	 **3-48**	65

Enones used: 2-cyclohexenone (**3-10**), 4-hexen-3-one (**3-12**)
Alkyl halides used: allyl bromide (**3-34**), benzyl bromide (**3-35**), hexyl iodide (**3-36**), bromoacetophenone (**3-37**), methyl bromoacetate (**3-38**)

since the high degree of oxygenated functionality of carbohydrates provide the synthetic chemist chiral starting

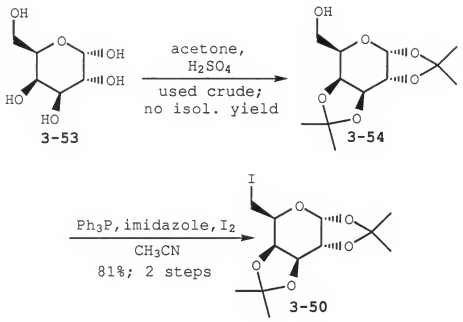
materials which can be utilized in the synthesis of complex and chiral products.

First the two iodinated sugars must be synthesized. As shown in Scheme 3-7, the secondary alcohol functionalities in D-ribose **3-51** were protected to provide isopropylidene **3-52**.[51] The anomeric alcohol was also protected to a methyl



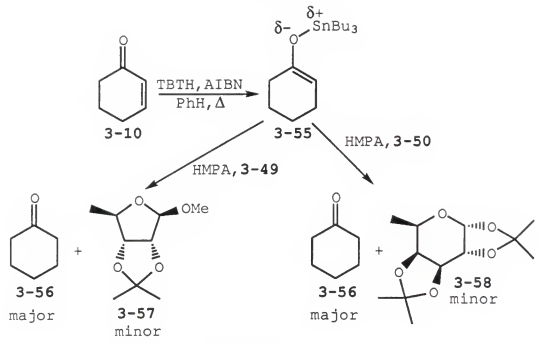
Scheme 3-7

ether in this step. This greatly improved the compound's solubility in nonpolar organic solvents used in the TBTH reaction. The remaining free alcohol was transformed to an iodide in the following step to afford **3-49**. Similarly, D-galactose **3-53** was protected[52] to its isopropylidene **3-54** and iodinated identically to the previous example to provide **3-50** (Scheme 3-8).



Scheme 3-8

It was now possible to attempt the free radical initiated alkylation reaction between an α,β-unsaturated ketone and the sugar derivatives. The reactions were carried out identically to the previously described alkylation procedure. That is, cyclohexenone **3-10** was reacted with TBTH under radical conditions to form the tin(IV) enolate **3-55** (Scheme 3-9). After HMPA and the desired sugar iodide derivative had been added, the reaction was allowed to reflux for three times as long as was necessary to complete the other alkylation examples (*ca.* 36 h). The only isolated products in both reactions were cyclohexanone (the reduced cyclohexenone) **3-56**, and a very small amount of the reduced sugar derivative **3-57** and **3-58**. Thus, the enolate had

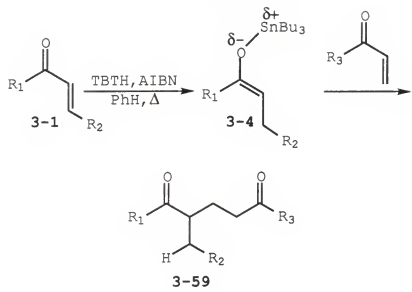


Scheme 3-9

presumably formed, but it was not reactive enough to react with the dense functionality present in the sugar systems.

Michael Reaction

In a final attempt to show the synthetic utility of the allylic O-stannyl ketyl intermediate, conjugate additions were studied. That is, the tin(IV) enolate **3-4** resulting from reaction of an enone **3-1** and TBTH was quenched with another enone to afford Michael product **3-59** (Scheme 3-10). This was originally attempted by forming the tin enolate *in situ* as in all of the previous examples and simply adding the unsaturated carbonyl quench neat. This proved to be unsuccessful as no reaction occurred. Next, HMPA was added

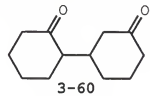
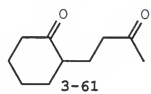
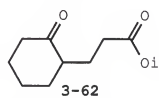


Scheme 3-10

before the quench since this additive drastically improved the yields in the alkylation experiments discussed earlier. A large amount of polymeric products were isolated using this strategy.

To suppress the polymerizations (presumably anionic) from occuring, the unsaturated quench was diluted to 0.5M in benzene and added slowly via addition funnel. The desired Michael products were observed using these conditions but only in modest yields. The results are shown in Table 3-3.[31] Unsuccessful attempts to improve yields such as higher dilution, reverse addition of HMPA and the unsaturated quench, and addition of HMPA via addition funnel were made. The major products using the optimum conditions and the attempted improvements were polymeric in nature.

Table 3-3
Michael reaction results

Enone	Activated Alkene	Product	Yield (%)
		 **3-60**	41
	Methylvinyl Ketone	 **3-61**	31
	Isodecyl Acrylate	 **3-62**	38

Conclusion

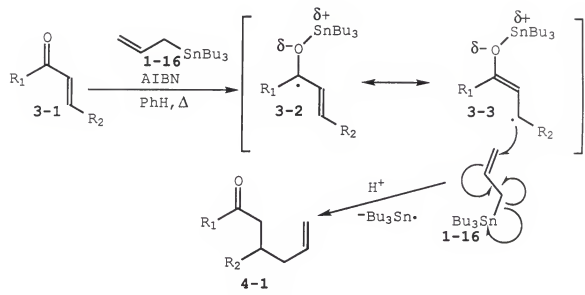
A new method for generating tin(IV) enolates has been developed. The enolate can be quenched with an aldehyde to form aldol products, or an alkyl halide to form alkylated products, or with enones to form conjugate addition products. The reaction is regioselective and chemically neutral which directly contrasts current highly basic methods to form enolates which rely on LDA, LHMDS, and dissolving metal reductions. The interesting combination of free radical and enolate chemistry required in this reaction exemplify the newly-emerging class of sequential one and two electron reactions.[53]

CHAPTER 4
FREE RADICAL-BASED CARBON-CARBON BOND FORMING REACTIONS VIA REACTION OF ENONES WITH A 2-SUBSTITUTED ALLYL STANNANE

As discussed previously, the reaction of an enone with TBTH provides two reactive centers via the allylic O-stannyl ketyl species. In Chapter 3, we were able to utilize the enolate site quite effectively, but the β-radical site only participated in hydrogen atom abstraction from TBTH to form a new carbon-hydrogen bond. The next synthetic goal was to utilize the radical site in an intermolecular carbon-carbon bond forming reaction. To accomplish this task, the TBTH reagent should be modified such that it could introduce a carbon-based substituent rather than a hydrogen to the β-position of an enone. This chapter focuses on the synthesis of a suitable tin reagent and its application in forming new carbon-carbon bonds from enone precursors under free radical conditions.

One of the more commonly used organotin reagents is allyltributyltin.[11] As explained in Scheme 1-6 (Chapter 1), allyltributyltin facilitates alkyl radical addition reactions where the resulting intermediate undergoes β-elimination to afford an allylated product and the regenerated tributyltin radical. We were hoping that allyltributyltin could be utilized to allylate an enone in a similar reaction (Scheme

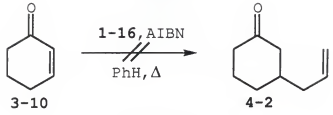
4-1). We envisioned the formation of the resonance stabilized allylic O-stannyl ketyl **3-2** ↔ **3-3** from the reaction of enone **3-1** with **1-16** under free radical



Scheme 4-1

conditions. If the β-radical in **3-3** added to another molecule of **1-16**, this would trigger β-elimination of tributyltin radical and produce allylated product **4-1**.

The reaction was attempted using identical free radical methodology described in Chapter 3. Specifically, cyclohexenone **3-10** was reacted with allyltributyltin (**1-16**) and AIBN. The reaction was refluxed for one day, but no formation of the desired allylated **4-2** was realized; only starting materials were isolated. The allyltin reagent simply would not undergo addition to the enone, thus the conditions for a successful free radical reaction were not present in this first attempt.



Scheme 4-2

It was observed that the intermediate β-radical species was quite nucleophilic in nature. Most alkyl radicals are inherently nucleophilic, but this particular radical species **4-3** contained a minor resonance contributor **4-4** which could further enhance the β-site's nucleophilicity (Figure 4-1). Therefore, it was determined that the radical was possibly too nucleophilic to add to the electron-rich double bond of allyltributyltin.

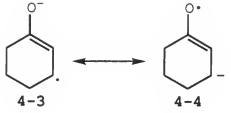
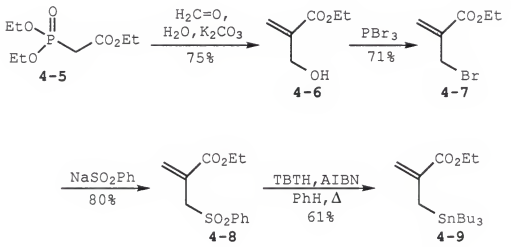


Figure 4-1

In order to make the double bond of the allyltin reagent less electron-rich, an electron-withdrawing substituent on the alkene was envisioned. We chose the ethyl ester substituent since there was a literature preparation of these tin reagents from benzenesulfonyl precursors.[54] The synthesis of this reagent can be seen in Scheme 4-3.

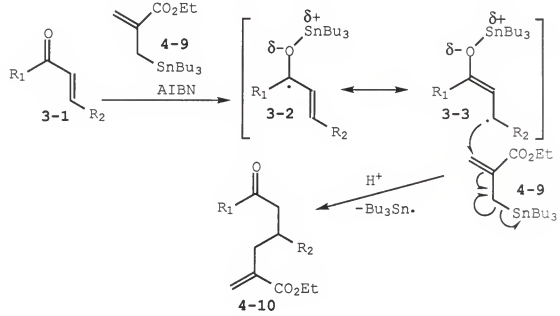
Specifically, triethyl phosphonoacetate (**4-5**) was reacted with an aqueous formaldehyde solution and potassium carbonate to afford Wittig/Horner elimination product **4-6**. This alcohol was reacted with phosphorus(III) bromide to produce the corresponding bromide **4-7**.[55] Following a reaction with benzenesulfinic acid, sodium salt, the benzenesulfinylmethylacrylate **4-8** was reacted with two equivalents of TBTH under free radical conditions to produce the desired tin reagent **4-9**.[54] The latter reaction probably proceeded by hydrostannylation of tributyltin radical across the acrylate double bond and then elimination of the $PhSO_2$ radical as described in Scheme 1-5 of Chapter 1.



Scheme 4-3

With the desired 2-substituted allyl stannane **4-9** synthesized, it was now possible to study its reactivity with enones. The reaction was envisioned to proceed through the sequence represented in Scheme 4-4. Enone **3-10** can react

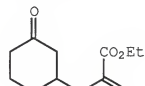
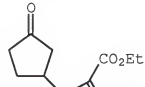
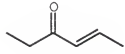
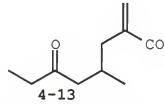
with **4-9** under free radical conditions to produce the resonance stabilized O-stannyl ketyl species **3-2** ↔ **3-3** as we have discussed previously. We hoped that the β-radical would add to the electron-deficient allyltin species **4-9** and trigger β-elimination of tributyltin radical which would provide allylated product **4-10**. The regenerated tin radical species could then continue the radical chain reaction.



Scheme 4-4

Three enones were subjected to this new reaction and the results are shown in Table 4-1. The reactions proceeded more slowly than the corresponding TBTH reactions in Chapter 3. Remember, in the TBTH reactions, we were able to observe consumption of the enone precursor by TLC, and this process typically took *ca.* 4 h. In the allylation reactions, some enone starting material was present by TLC even after 14 h.

Table 4-1
β-Radical allylation results

Enone	Product	Yield (%)
3-10	 **4-11**	61
3-11	 **4-12**	58
 **3-12**	 **4-13**	65

Additional AIBN did not seem to speed up the reaction. In fact more tin-based byproducts were observed when additional aliquots of AIBN were added, therefore, the overall yield of allylated product was lowered somewhat due to deleterious consumption of **4-9**.

There is one other issue which should be addressed in this chapter; it concerns the enolate reactive site in these molecules. After the enone β-radical adds to **4-9** and eliminates the tributyltin radical, the enolate should still be present in the molecule. Our results in Table 4-1 show that the enolate was presumably quenched by either moisture

in the air or certainly by column chromatography. We were aware that an ester group was located five carbons away as in compound **4-14** and could possibly react with the enolate in a Claisen reaction (Figure 4-1). Scheme 2-3 in Chapter 2 clearly demonstrated that a tin enolate reacted intramolecularly with an ester to give the minor Claisen product. This did not occur in the reactions in this chapter probably due to ester conjugation with an alkene. The olefin adds stability to the ester and thereby makes it less reactive. We even tried to activate the enolate by adding HMPA, which improved the reactivity in Chapter 3, but no Claisen product was realized. The enolate could also react in a conjugate addition reaction (**4-15** in Figure 4-1) except that this process would violate Baldwin's rules concerning 5-endo-trig cyclizations. Intermolecular Michael additions with tin enolates, in marked contrast, were successful in Chapter 3.

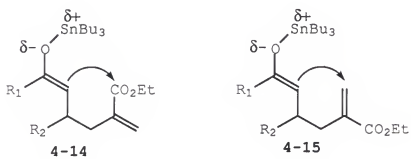


Figure 4-1
Possible intramolecular reactions of the tin enolate

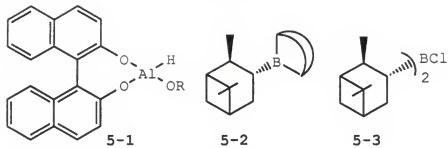
Novel methodology for forming new carbon-carbon bonds at the β-position of enones has been introduced. In addition, we now have further proof of our proposed mechanism of tin radical promoted reactions with enones. That is, the proposed β-radical species **3-3** does exist and can not only abstract a hydrogen atom from TBTH as previously demonstrated, but also add intermolecularly to an electron-deficient olefin. A 2-substituted allyl stannane can be used to stimulate the formation of the β-radical reacting species from enone precursors as well as the adding olefin. We hope that this chemically neutral method can be used in the synthesis of more complex molecules, thereby becoming an important synthetic tool to the organic chemist.

CHAPTER 5
SYNTHESIS OF SEVERAL MIXED (-)-MENTHYLTIN HYDRIDES AND THEIR APPLICATION TO ASYMMETRIC, FREE RADICAL-BASED REDUCTIONS

Introduction

As recently as the 1960s, asymmetric synthesis was considered by many chemists to be a curiosity. When the Food and Drug Administration determined that many side-effects of pharmaceutical products were in fact due to enantiomeric impurities, the field of study increased dramatically.[56] Asymmetric synthesis has received immense attention over the past few years.[57] Presently, all conceivable methods that produce optically pure chiral molecules are being aggressively studied by both industrial and academic institutions.

One of the many asymmetric reactions that has received enormous attention is the enantioselective reduction of prochiral ketones.[58] Three of the more popular chiral reducing agents (Figure 5-1) are Noyori's BINAL-H **5-1**, Midland's Alpine-Borane **5-2**, and Brown's DIP-Chloride **5-3**.[58,59] These reagents are successful in inducing enantioselective reactions, because they lead to a chiral transition state where reduction can only take place from one face of the ketone.



5-1 **5-2** **5-3**

Figure 5-1
Universal chiral reductants

The reduction of ketones with TBTH (Scheme 1-10 and Scheme 1-11 in Chapter 1) produces an achiral alcohol. This is because the tributyltin hydride reagent has no chiral atmosphere. If the butyl ligands in TBTH (**1-3**) were replaced with one or more chiral ligands as in **5-4**, it could now possibly induce enantioselective transformations (Scheme 5-1).

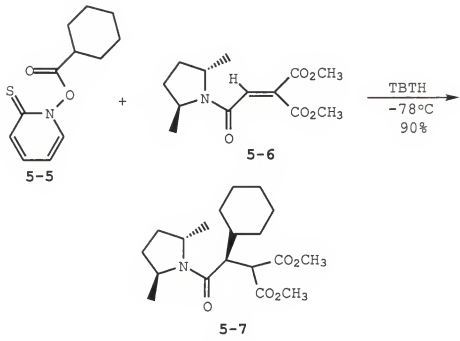
1-3 **5-4**

***R** = chiral ligand

Scheme 5-1

Ketone reductions with **5-1**, **5-2**, and **5-3** are the result of enantioselective $2e^-$ reductions. Free radical processes can also be used in reductions, but enantioselective hydrogen atom reductions (H•) under free radical conditions are very

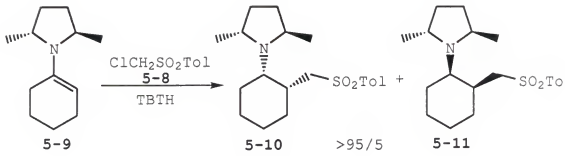
poorly understood. The absolute stereochemistry of free radical reactions has only recently been studied in detail over the last 6-8 years, and examples of nonracemic free radical reactions are scarce.[19] Nearly all of the existing attempts at enantioselective free radical transformations use a chiral auxiliary.[19] Porter discovered that the Barton ester of cyclohexyl carboxylic acid **5-5** reacted with the chiral auxiliary olefin **5-6** and TBTH to give 90% of one diastereomer (Scheme 5-2).[60] Renaud not only developed the TBTH mediated free radical addition of electrophilic radical addition to



5-5 + **5-6** → **5-7**

Scheme 5-2

enamines, but also utilized a chiral auxiliary group to control the stereochemistry.[61] Specifically, radical addition of **5-8** to the chiral auxiliary enamine **5-9** provided



Scheme 5-3

essentially **5-10** instead of the other possible cis stereoisomer **5-11** (Scheme 5-3). There was no trans product observed. Although the use of chiral auxiliaries is successful, their application is somewhat inelegant in that extra synthetic steps are required to introduce it to the molecule and to remove it.

As discussed chapter 1, there are two pathways through which TBTH can reduce ketones. The desired mechanism can easily be discerned by the choice of reaction conditions. Under Lewis acid conditions, the true hydride donor mechanism prevails, whereas under free radical conditions, a ketyl is formed before hydrogen atom abstraction.[11] It is important to note that we weren't interested in the chiral tin hydride behaving as a true hydride donor, because as stated earlier, there are already numerous chiral hydride donors available to the organic chemist. We were interested in the development of the first free radical-based chiral hydride source. At the beginning of this project, we were unaware of any such reagents that had been successfully applied in the asymmetric

reduction of ketones. While this work was in progress, a South American group developed a conceptually related approach.[62,63]

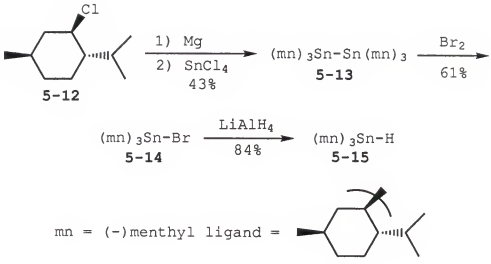
This chapter focuses on the syntheses of several chiral tin reagents as well as their application in the asymmetric reduction of ketones. We hoped to demonstrate the applicability of the tin ketyl species in enantioselective reductions.

Syntheses and reductions

The first item of consideration in the synthesis of a chiral tin hydride was the selection of a suitable chiral ligand to attach to the tin atom. The ligand should of course be chiral, and the location of the chiral center or centers should be as close in proximity to the Sn-H bond as possible. Also, the Sn-C bond between the tin atom and the chiral ligand must be configurationably stable. After careful consideration and literature searching, it was decided that the (-)-menthyl ligand would be used. Besides economic advantages, it bonds to a tin atom with a completely predictable stereochemistry using a Grignard method reported by Schumann.[64]

The first logical chiral tin hydride to synthesize was one that contained as many chiral (-)-menthyl ligands as possible, therefore, tri-(-)-menthyltin hydride was prepared. Specifically, (-)-menthylmagnesium chloride (prepared from (-)-menthyl chloride **5-12** and magnesium metal) was added to tin

tetrachloride to provide hexa-(-)-menthylditin **5-13** (Scheme 5-4).[65] When this compound was reacted with one equivalent of bromine, tri-(-)-menthyltin bromide **5-14** was formed.[65] Tri-(-)-menthyltin hydride **5-15** was then easily prepared by reacting bromide **5-14** with lithium aluminum hydride.

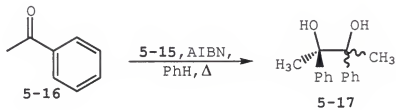


Scheme 5-4

With the first generation chiral tin hydride prepared, it was time to study its asymmetric reducing ability. First, a suitable ketone should be selected. Acetophenone was chosen since many chiral reducing agents are successful in promoting the asymmetric reduction of this ketone.[58] Thus, the optical rotation of the chiral alcohol was well documented; both enantiomers of phenylethanol are even commercially available from the Fluka Chemical Corporation.

The reduction was carried out by methods similar to most

of the TBTH reactions described in this dissertation. As shown in Scheme 5-5, acetophenone **5-16**, AIBN, and tri-(-)-menthyltin hydride **5-15** were dissolved in benzene and refluxed until no ketone was present by TLC. This procedure is called method A in the experimental section. The major product that formed was not the alcohol, but instead the pinacol product **5-17**. Thus, the first step of free radical ketone reduction, the formation of a tin ketyl, did occur, but the second step, hydrogen atom abstraction from the chiral tin, did not. It was obvious that ketyl coupling

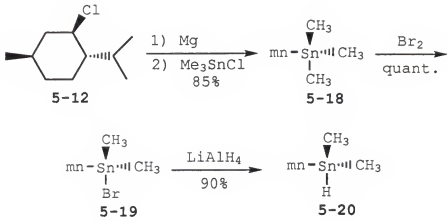


Scheme 5-5

leading to the pinacol product was faster than hydrogen atom abstraction. It was presumed that the sterically encumbered tri-(-)-menthyltin hydride **5-15** was too hindered to deliver the hydrogen atom. We were also disappointed to learn that the pinacol was optically inactive. Thus, three (-)-menthyl ligands might be too many, therefore, another molecule containing less steric bulk was synthesized.

It was decided that a better point of origin for this project should be a chiral tin reagent which only contains one (-)-menthyl ligand and little steric bulk. Thus, (-)-menthyldimethyltin hydride **5-20** was synthesized (Scheme 5-6).

Specifically, (-)-menthylmagnesium chloride (prepared from (-)-menthyl chloride **5-12** and magnesium metal) was added to trimethyltin chloride to produce (-)-menthyltrimethyltin **5-18**.[64] One methyl group was selectively cleaved with one

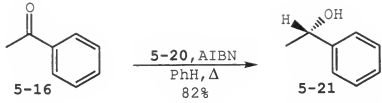


Scheme 5-6

equivalent of bromine to afford (-)-menthyldimethyltin bromide **5-19**.[64] Upon reaction with lithium aluminum hydride, bromide **5-19** was reduced to (-)-menthyldimethyltin hydride **5-20**.

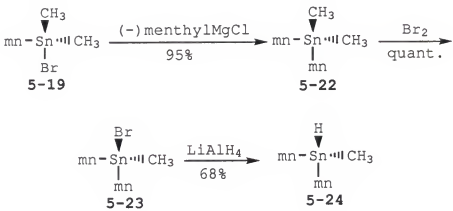
The reduction of acetophenone (Method A) was carried out (Scheme 5-7) identically to the previous example. The chiral tin reagent **5-20** reduced acetophenone to 1-phenylethanol **5-21** in 82% yield. Unfortunately, very little evidence of asymmetric induction was observed as the (-)-(S)-antipode was favored only by less than 5%. No pinacol product was isolated from this reaction.

Since three (-)-menthyl ligands as well as one (-)-menthyl ligand had been attempted, it was a logical



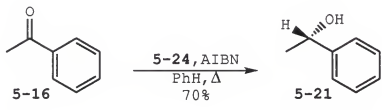
Scheme 5-7

progression to prepare a tin hydride with two (-)-menthyl ligands. Thus, methyldi-(-)-menthyltin hydride **5-24** was synthesized (Scheme 5-8). This process reacted (-)-menthylmagnesium chloride with (-)-menthyldimethyltin bromide **5-19**, which had already been prepared in the previous synthesis in Scheme 5-6, to form dimethyldi-(-)-menthyltin **5-22**. One of the methyl groups was cleaved with bromine to provide methyldi-(-)-menthyltin bromide **5-23**. Bromine reduction was accomplished with lithium aluminum hydride to afford methyldi-(-)-menthyltin hydride **5-24**.



Scheme 5-8

As seen in Scheme 5-9, the reduction of acetophenone **5-16** with this chiral tin reagent (method A) again afforded 1-phenylethanol **5-21** in good yield, but the enantiomeric excess of the (-)-(S)-antipode had improved to 8%. This was not the dramatic improvement in asymmetric induction that was desired, but it was a slight increase nonetheless.



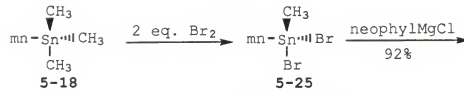
Scheme 5-9

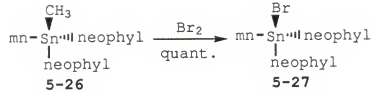
At this juncture, it was discovered that we weren't alone in our search for a chiral tin hydride which could be used in asymmetric free radical-based reductions. In 1995 Podesta and co-workers[62] in South America published two examples of the asymmetric reduction of acetophenone with a chiral tin hydride. The two tin regents he used were dineophyl-(-)-menthyltin hydride and (-)-menthyldimethyltin hydride. He had obtained ee's of 40% and 7% respectively when the reduction of acetophenone was performed. The relatively low 7% ee that Podesta obtained using (-)-menthyldimethyltin hydride was not surprising; this was nearly identical to the results we observed with this compound (discussed previously in Scheme 5-6). In our hands,

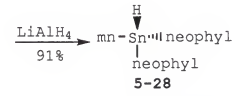
an ee of less than 5% (discussed previously in Scheme 5-7) was obtained. It is significant that Podesta's reduction procedure was somewhat different than ours in that the radical reduction was carried out under photochemical conditions rather than the thermal methods we had used. This method will be discussed later in this chapter.

Podesta's 40% ee using dineophyl-(-)-menthyltin hydride was especially interesting and surprising, since this was significantly higher than any of the ee's we had obtained. It was decided that an attempt should be made to repeat this finding, thus, the tin reagent must first be prepared. A method more expedient than Podesta's route was used to synthesize the desired dineophyl-(-)-menthyltin hydride. Precursor **5-18**, which could be used to prepare this compound, had previously been synthesized in one of our earlier efforts. Specifically, (-)-menthyltri-methyltin **5-18** was reacted with two equivalents of bromine to provide (-)-menthylmethyltin dibromide **5-25**, which was directly reacted with excess neophylmagnesium chloride to afford methyldineophyl-(-)-menthyltin **5-26** (Scheme 5-10). Cleaving the methyl group with bromine provided dineophyl-(-)-menthyltin bromide **5-27**. Subsequent bromide reduction with lithium aluminum hydride formed dineophyl-(-)-menthyltin hydride **5-28**.

The reduction of acetophenone was carried out identically to Podesta's work.[62] As seen in Scheme 5-11, after irradiating a neat mixture of acetophenone **5-16**, AIBN,

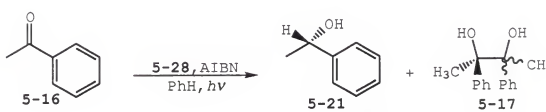






Scheme 5-10

and **5-28** for 24 h using a Hanovia 450W medium pressure Hg-vapor lamp (method B), the resulting 1-phenylethanol **5-21** was isolated. The yield (40%) was better than Podesta's yield



Scheme 5-11

(28%), but the ee was significantly lower (6% as compared to Podesta's 40%). A small amount of pinacol **5-17** was also isolated. Curiously, Podesta did not mention pinacol formation.

The analytical factor of reaction temperature should be addressed. After 24 h of irradiation, the Pyrex reaction test tube had heated to a point where it was difficult to touch. If the tube is placed in a beaker of ice during the reduction, the ice melts in a period of 2-3 h. Thus, a method for keeping the tube cool for 24 h had to be developed. There are large scale cooling apparatus that are used effectively in photochemical reactions, but there are no micro scale photochemical cooling apparatus possessed by any research groups in the UF Chemistry Department. An apparatus was made that would accomplish this task (Figure 5-2). The reduction of acetophenone was attempted again using the cooling apparatus, but whereas the yield improved to 46%, the ee remained low. (The ee did improve very slightly to 6.2%, but this result was considered negligible.)

Podesta had some concern in his isolation of the reduced products. He mentioned that although water was added at the end of the reaction to liberate the alcohol, many of his chromatographic fractions were contaminated with the organotin alkoxide.[62] Knowing this before we ran the reaction, we diluted the reaction mixture with benzene at the end of the reaction, added a 5% aqueous hydrochloric acid solution, and allowed this mixture to stir for a few minutes.

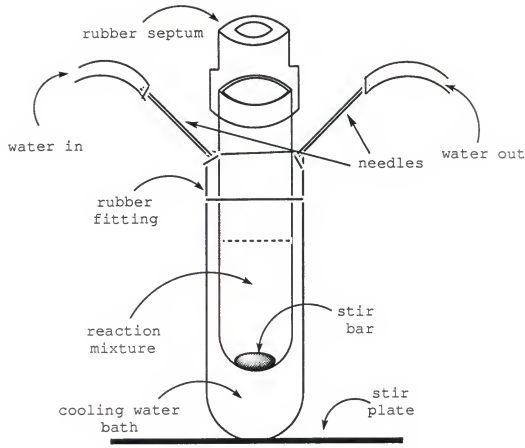


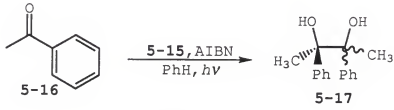
Figure 5-2
Apparatus used to cool photochemical reactions

This method totally cleaved all tin-oxide bonds, consequently, no organotin alkoxide was isolated.

The explanation in the discrepancy between our results and Podesta's results could be attributed to this change in workup. Obviously, since there exists a chiral (-)-menthyl ligand on the tin atom, the corresponding organotin alkoxide would contain chirality as well. This impurity would have an optical rotation of its own, thus intensifying the observed rotation. It was possible that Podesta had some of these

chiral impurities in his isolated alcohol product, therefore, his reported ee's should be accepted with skepticism.

The new procedure (method B) was applied to the reduction previously performed which did not yield the desired alcohol product. As discussed in Scheme 5-5, the reduction of acetophenone with tri-(-)-menthyltin hydride **5-15** led to the formation of pinacol product **5-17**. The identical reaction was attempted again using the photochemical method B (Scheme 5-12). We were discouraged to find that the pinacol product **5-17** was once again the only isolated product. It was at this point where the project was terminated.



Scheme 5-12

Approximately one month after stopping work on the chiral tin hydride project, another Podesta paper was published.[63] This work was similar in scope and included the synthesis of methyldi-(-)-menthyltin hydride and its reduction of acetophenone under photochemical conditions. We had previously made this molecule **5-24** (see Scheme 5-8) and reduced acetophenone (see Scheme 5-9) as well. Even though thermal method A was used in our work, the results were strikingly similar. Using photochemical method B, Podesta

obtained (-)-(S)-phenylethanol (69% yield) with an ee of 8.8%.[63] Recall that our reaction provided (-)-(S)-phenylethanol (70% yield) with an ee of 8%. It was also interesting that in Podesta's most recent studies, he had seemingly solved the problem of the unwanted organotin alkoxide impurity by dissolving the post-reaction mixture in diethyl ether, adding a 1M solution of acetic acid in diethyl ether, and stirring for 2 h.[63] It is unfortunate that this simple procedure was not utilized in his previous work.

Conclusion

An attempt has been made to develop the first free radical-based asymmetric reduction of prochiral ketones. Several chiral tin hydrides containing (-)-menthyl ligand(s) have been synthesized. The preparations used in this project ranged from modest to excellent yields. Their utility in the asymmetric reduction of acetophenone was also studied. The results show that there is very little asymmetric induction produced by these compounds in the free radical-based reductions. It was significant though that every reduction which yielded the desired alcohol product favored the (-)-antipode. It was discovered that we were not alone in our search, therefore, not alone in our disappointment. Much research in this unknown area needs to be performed.

CHAPTER 6
EXPERIMENTAL

General Methods

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). ^{1}H Nuclear magnetic resonance spectra were recorded on a Varian VXR-300 (300 MHz), a Varian Gemini-300 (300 MHz), and a General Electric QE-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the same spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane as an internal standard. All mass spectroscopy was performed by the Mass Spectroscopy Service at the University of Florida Department of Chemistry. Elemental analysis was performed by either the Elemental Analysis Service at the University of Florida department of Chemistry or by Atlantic Microlab Inc. in Norcross, GA. Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

All reactions were run under an inert atmosphere of argon using clean, flame dried reaction apparatus. All yields reported refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography (TLC). Solvents and reagents were distilled under inert atmospheres

from appropriate drying agents according to established procedures. All reactions involving tributyltin hydride were degassed with argon for at least 20 minutes prior to reflux.

Analytical TLC was performed using Kieselgel 60 F-254 precoated 0.25mm silica gel plates using UV light, phosphomolybdic acid in ethanol, or *p*-anisaldehyde in ethanol as an indicator. Column chromatography was performed by standard flash chromatographic techniques using Kieselgel silica gel 60 (230-400 mesh). Gas chromatograph (GC) experiments were performed on a Varian 3500 capillary gas chromatograph using a J & W fused silica capillary column (DB5-30W; film thickness 0.25 μm).

Experimental Procedures

4,6-Heptadienoic Acid (**2-13**)

Triethyl orthoacetate (28.9 g, 0.178 mol) was added to a benzene solution (40 mL) containing 1,4-pentadien-3-ol (5 g, 0.06 mol) and propionic acid (170 mL, 2.3 mmol). The mixture was refluxed for 16 h; the solvents and residual starting materials were removed by distillation. The resulting ester was hydrolyzed (25% KOH/methanol, reflux 2.5 h) directly to give 5.86 g (78%) of acid **2-13**: IR (neat) 3070, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.9 (s, 1 H), 6.5-4.8 (m, 5 H), 2.5-2.3 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 179.7, 136.7, 132.3, 132.1, 115.9, 33.5, 27.4.[33]

4,6-Heptadienoyl-chloride (**2-14**)

A 0.23M solution of acid **2-13** (5.0 g, 0.04 mol in 170 mL hexanes) was refluxed with oxalyl chloride (10.4 mL, 120 mmol) for 7 h. Hexane and excess oxallyl chloride were distilled under reduced pressure to yield **2-14** (4.23 g; 74%) as a yellow oil: IR (neat) 1793 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.3-5.8 (m, 5 H), 3.0 (t, J = 9 Hz, 2 H), 2.5 (q, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 136.3, 133.2, 130.1, 116.6, 46.5, 27.8 (carbonyl peak not present in spectrum).[33]

1-Diazo-5,7-octadien-2-one (**2-15**)

Acid chloride **2-14** (13.7 g, 95 mmol) was added dropwise to an ethereal solution of diazomethane[66] at 0°C. The solution was permitted to stand overnight and was then boiled briefly to expel excess diazomethane. After concentration, a pale yellow oil was isolated from rapidly performed chromatography or silica gel to yield 13.05 g (92%) pure compound **2-15**: IR (neat) 2092, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.3 (s, 1 H), 6.3-5.0 (m, 5 H), 2.4 (m, H 4); ^{13} C NMR ($CDCl_3$) δ 193.9, 136.8, 132.6, 132.0, 115.7, 54.5, 40.1, 27.7.[33]

6β-Ethenyl-1,5β-bicyclo[3.1.0]hexan-2-one (**2-16**)

A 0.05M solution of diazoketone **2-15** (13.1 g; 0.087 mol in 1740 mL benzene) was refluxed overnight with 10wt% of copper(II) acetoacetonate (1.3g). After removal of the solvent, the residue was filtered through alumina, eluting

with methylene chloride. Further purification by column chromatography afforded compound **2-16** (7.5 g; 71%): IR (neat) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4-5.0 (m, 3 H), 2.0 (m, 5 H), 1.95 (m,1 H),1.8 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 213.1, 136.2, 114.6, 36.0, 32.3, 30.3, 29.0, 27.7.[33]

7-Hydroxy-1,5β-bicyclo[3.1.0]hexa-2-one ethylene ketal (**2-17**)

Ketone **2-16** (3.5 g, 0.029 mol) was protected to the ketal by reaction with ethylene glycol (4.61 g, 0.074 mol) and *p*-toluenesulfonic acid (catalytic amt.) in benzene (286 mL), refluxing with Dean Stark tube for 18 h. After quenching with sodium bicarbonate, extracting with ether, and evaporation, a portion of the crude ketal (750 mg, 4.52 mmol) was dissolved in ethanol (36 mL) and reacted with ozone. After starting material consumption (by TLC) had taken place, the resulting aldehyde was reduced directly with sodium borohydride (513 mg, 13.6 mmol) to the alcohol. After evaporation and purification by column chromatography, compound **2-17** was isolated (0.63 g; 82%, combined ozonolysis and reduction): IR (neat) 3418, 2943, 2879, 1336, 1105, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (m, 4 H), 3.5 (m, 2 H), 3.1 (broad s, 1 H), 2.0-1.2 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 118.1, 64.7, 64.5, 64.1, 31.4, 27.6, 24.3, 22.5, 21.5.

7-Oxoallyl-1,5 b-bicyclo[3.1.0]hexan-2-one (**2-18**)

Sodium hydride (60% in mineral oil, 79 mg; 3.29 mmol) was washed with pentane (3 X 4 mL) and suspended in THF (3.3

mL). Compound **2-17** (280 mg, 1.65 mmol) in THF (2.7 mL) was added to the sodium hydride solution at 0°C. After allowing the flask to warm to room temperature, allyl bromide (1.43 mL, 16.5 mmol) was added neat, and the reaction was allowed to run for 12 h. Reaction mixture was then poured onto ice and extracted with ethyl acetate. After evaporation, the crude ether was deprotected in a solution of acetone (22 mL) and a catalytic amount of *p*-toluenesulfonic acid. The reaction was quenched with sodium bicarbonate, extracted with ethyl acetate, and concentrated under reduced pressure. After chromatography, ketone **2-18** (0.173 g; 64%, 2 steps) was obtained: ^{1}H NMR ($CDCl_3$) δ 5.9 (m, 1 H), 5.3 (m, 2 H), 4.0 (m, 2 H), 3.3 and 3.5 (m, 2 H), 2.1 (broad m, 5 H), 1.7 (q, J = 2.5 Hz, 1 H), 1.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 134.5, 117.24, 117.2, 71.7, 70.5, 32.5, 32.4, 26.7, 26.3, 22.5.

Cyclized Furan (**2-19a** and **2-19b**)

To ketone **2-18** (40 mg, 0.24 mmol) was added tributyltin hydride (71.3 mL, 0.265 mmol), 2,2'-azobisisobutyronitrile (AIBN) (8 mg, 0.048 mmol), and benzene (2.4 mL). The reaction mixture was degassed and refluxed for 20 h, concentrated and purified by flash chromatography to yield diastereomers **2-19a** and **b** (0.030g; 73%): IR (neat) 2958, 2851, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.0-3.3 (m, 4 H), 2.9-1.2 (m, 9 H), 1.1 (d, J = 7 Hz), 1.05 (d, J = 7 Hz) (The two previously mentioned doublets integrated to 3 hydrogens

combined (methyl group) in a ratio of 1/1); High-resolution MS (EI): Calcd, 168.1150; found, 168.1129.

7-Oxoallyl-1,5β-bicyclo[3.1.0]hexan-2-one ethylene ketal (**2-23**)

THF (6 mL) was added to washed sodium hydride (123 mg, 5.1 mmol). Ketal **2-17** (58 mg, 3.42 mmol) in THF (6.25 mL) was added to the reaction mixture at 0°C. After allowing the flask to warm to room temperature, allyl bromide (2.96 mL, 34.2 mmol) was added neat, and reaction allowed to stir overnight. Following pouring the reaction mixture onto ice, the solution was extracted with ethyl acetate, concentrated under reduced pressure, and purified by column chromatography to yield ether **2-23** (0.59 g, 82%): ^{1}H NMR ($CDCl_3$) δ 5.9 (m, 1 H), 5.2 (m, 2 H), 4.0 (complex m, 6 H), 3.45 and 3.2 (m, 2 H), 1.9-1.2 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 135.0, 118.2, 116.9, 116.8, 116.7, 71.8, 71.4, 64.8, 64.1, 31.5, 27.5, 24.4, 22.1, 19.7.

Ketal (**2-24**)

Compound **2-23** (430 mg, 2.05 mmol) was dissolved in methylene chloride (17 mL) and reacted with ozone. Upon completion of reaction (by TLC) 2-3 drops of dimethyl sulfide was added to the reaction mixture. The resulting aldehyde was not purified given that it was only one spot on the TLC plate. It was reacted crude with methyl (triphenylphosphoranylidene)acetate (1.79 g ;0.0054 mol) in methylene chloride

(3.6 mL) at room temperature for 12 h. Four products were observed. Two of the products were the desired cis and trans isomers of compound **2-24**, and the other two were the deprotected cis/trans compounds. Yield was thus calculated in next step which luckily was a deprotection. Cis/trans ketal **2-24**: ^{1}H NMR ($CDCl_3$) δ 6.9 (d of t, J = 15 Hz, 4 Hz, 1 H), 6.45 (d of t, J = 10 Hz, 4 Hz, 1 H), 6.05 (d of t, J = 15 Hz, 2 Hz, 1 H), 5.85 (d of t, J = 10 Hz, 2 Hz, 1 H), 4.6 (m, 2 H), 4.1 (m, 2 H), 4.0-3.8 (m, 8 H), 3.68 (s, 3 H), 3.65 (s, 3 H), 3.4-3.1 (m, 4 H), 2.0-1.1 (m, 14 H).

Ketone (**2-25**)

Due to the fact that most of the ketal was removed in previous step, an undetermined amount of ketal **2-24** was dissolved in acetone (20 mL) with a catalytic amount of *p*-toluenesulfonic acid. That is, the starting material used in this reaction was a mixture of ketal **2-24** and ketone **2-25**. After total deprotection (by TLC), the mixture was quenched with sodium bicarbonate, extracted with ethyl acetate, concentrated, and purified by column chromatography. Cis/trans ratio was obtained by GC (Varian 3500) and found to be 52/48. The yield of combined cis/trans products **2-25** was 0.224 g (49%, 3 steps; calculated with respect to **2-23**). Cis/trans **2-25**: ^{1}H NMR ($CDCl_3$) δ 6.9 (d of t, J = 15, 4 Hz, 1 H), 6.45 (d of t, J = 10, 4 Hz, 1 H), 6.05 (d of t, J = 15, 2 Hz, 1 H), 5.85 (d of t, J = 10, 2 Hz, 1 H), 4.55 (m, 2 H), 4.15 (m, 2 H), 3.75 (s, 3 H), 3.7 (s, 3 H), 3.3-3.5 (m, 4

H), 1.0-2.1 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 148.0, 147.90, 144.05, 121.09, 121.07, 121.04, 119.3, 71.1, 69.2, 68.6, 51.5, 51.3, 32.5, 32.31, 32.3, 26.6, 26.5, 26.1, 26.0, 22.5; Cis **12**: ^1H NMR ($CDCl_3$) δ 6.45 (d of t, J = 10 Hz, 4 Hz, 1 H), 5.85 (d of t, J = 10 Hz, 2 Hz, 1 H), 4.55 (m, 2 H), 3.7 (s, 3 H), 3.5-3.3 (m, 2 H), 2.1-1.0 (m, 7H); Trans **12**: ^1H NMR ($CDCl_3$) δ 6.9 (d of t, J = 15, 4 Hz, 1 H), 6.05 (d of t, J = 15, 2 Hz, 1 H), 4.15 (m, 2 H), 3.75 (s, 3 H), 3.5-3.3 (m, 2 H), 2.1-1.0 (m, 7 H); High-resolution MS (M + 1): Calcd, 225.1049; found, 225.1129.

2-Cyclopentene-1-ol (**2-29**)

Commercially available cyclopentenone **2-28** (3.5 g, 0.043 mol) was dissolved in previously prepared 0.4M solution of cerium(III) chloride (15.9 g, 0.043 mol) in MeOH (107 mL). Sodium borohydride (1.61 g, 0.043 mol) was added slowly over a 2 minute period. Reaction was completed in 5 min (TLC). After quenching with water, the mixture was extracted with ether, dried with sodium sulfate, concentrated, and purified by column chromatography to afford alcohol **2-29**: ^1H NMR ($CDCl_3$) δ 6.0 (m, 1 H), 5.8 (m, 1 H), 4.8 (m, 1 H), 2.9 (broad s, (OH)), 2.5 (m, 1 H), 2.2 (m, 2 H), 1.7 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 134.6, 133.4, 76.7, 33.1, 30.9, 14.0.[36]

2-Cyclopentene-1-diazo ester (**2-31**)

Glyoxylic acid chloride *p*-toluenesulfonyl hydrazone **2-34** (830 mg, 3.18 mmol) was added to an ice-cooled solution of

alcohol **2-29** (143 mg, 1.7 mmol) in distilled methylene chloride (9.8 mL) under an argon atmosphere. Dimethylaniline (0.39 mL, 3.12 mmol) was added and the mixture was stirred 15 min. Triethylamine (1.21 mL, 8.73 mmol) was added and the reaction was allowed to stir 10 min at 0°C, then 15 min at room temperature, before water (6.8 mL) was added. The mixture was concentrated *in vacuo*. Saturated citric acid (13.6 mL) and 10% ethyl acetate-hexanes (5.5 mL) was added and the aqueous layer was extracted with an additional aliquot of 10% ethyl acetate-hexanes (6 mL). The organic layers were combined, washed with saturated citric acid (5.6 mL), dried over sodium sulfate, and concentrated to yield 0.191 g (74%) crude compound **2-31**: IR (neat) 3123, 2112, 1701, 1253, 1105cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.1 (m, 1 H), 5.8 (m, 2 H), 4.75 and 4.68 (s, 1 H), 2.4 (m, 4 H), 1.8 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.6, 129.2, 81.0, 46.2, 31.0, 29.8.[37]

Glyoxylic acid p-toluenesulfonylhydrazone (**2-33**)

A solution of glyoxylic acid **2-32** (10 g; 0.109 mol) in of water (100 mL) was warmed in an Erlenmeyer flask to 60°C. The solution was treated with a 60°C solution consisting of *p*-toluenesulfonylhydrazide (20.2 g; 0.109 mol) in 2.5M hydrochloric acid (55 mL). Mixture was stirred until hydrazone solidified. The solution was then allowed to stand in a refrigerator overnight. Product was then recrystallized with carbon tetrachloride/ethyl acetate to afford **2-33** (20.9 g; 79%) as white crystals: m.p. 149-152 °C.[38]

p-Toluenesulfonylhydrazone of glyoxylic acid chloride (**2-34**)

Acid hydrazone **2-33** (20.9 g, 0.086 mol) was dissolved in benzene (104 mL) and thionyl chloride (freshly distilled) (12.5 mL; 170 mmol). The mixture was refluxed for 2 h, cooled immediately, and filtered through a Celite mat. After concentration, the residual solid was mixed with benzene (18 mL) warmed and chopped into a fine suspension. The suspension was cooled, filtered and recrystallized using benzene/ligroin. After, acid chloride **2-34** (15.8 g;70%) was isolated as pale yellow prisms: m.p. 100-108°C.[38]

Cyclopropyl lactone (**2-35**)

Diazoester **2-31** (190 mg, 1.25 mmol) in toluene (27 mL) was added dropwise via addition funnel to a refluxing solution of bis-(N-t-butylsalicylaldiminato) copper (II)[39] (28 mg, 0.068 mmol) in toluene (27 mL). After the addition was complete, the solution was allowed to reflux for an additional 30 min, cooled, concentrated, and purified by column chromatography to yield **2-35** (0.13 g; 81%) existing as a colorless oil: IR (neat) 1758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.0 (t, J = 2 Hz, 1 H), 3.0 (q, J = 5 Hz, 1 H), 2.25-1.7 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 84.2, 40.3, 35.1, 28.4, 28.3, 23.2.[37]

7-Hydroxy-1,5β-bicyclo[3.1.0]hexan-2-ol (**2-36**)

Cyclopropyllactone **2-35** (213 mg, 1.72 mmol) was dissolved in methylene chloride (3.44 mL), and the flask was

cooled to -78°C. A 1M solution of diisobutylaluminumhydride (DIBAL) in hexane (6.88 mL, 6.88 mmol) was added dropwise, and the flask was allowed to warm slowly to room temperature. The reaction solution was again cooled to -78°C and quenched with 2-3 drops of methanol. Rochelle's salt (20 mL of a saturated solution) along with ethyl acetate (40 mL) was poured into reaction mixture and allowed to stir vigorously for 2 h. The organic layer was concentrated and the product was purified by column chromatography to yield diol **2-36** (0.194 g; 88%): ^{1}H NMR ($CDCl_3$) δ 4.8 and 4.1 (m, 2 H), 3.6 (d of d, J = 10, 9 Hz, 2 H), 2.2-0.9 (complex m, 7 H); ^{13}C NMR ($CDCl_3$) δ 74.8, 58.5, 34.1, 28.0, 24.0, 23.9, 22.82, 22.77.

Allyloxy ether (**2-39**)

THF (1 mL) was added to washed sodium hydride (26 mg, 1.07 mmol). Diol **2-36** (105 mg, 0.82 mmol) in THF (1 mL) was added dropwise at 0°C. The reaction flask was allowed to warm to room temperature, and allyl bromide (0.11 mL, 1.23 mmol) was added neat. The reaction was allowed to run 20 h before all the starting material was consumed. Upon completion, the reaction mixture was poured onto ice, extracted with ethyl acetate, concentrated, dried with sodium sulfate, and purified by column chromatography. Ether **2-39** (0.1 g; 73%) was isolated as a pale yellow oil as a mixture of 2 diasteriomers: ^{1}H NMR ($CDCl_3$) δ 5.9 (complex m, 1 H), 5.3 (complex m, 2 H), 4.6 and 4.5 (m, 1 H), 4.0 and 3.6 (m, 4 H), 3.25 (broad s, (OH)), 2.2-1.0 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ

134.4, 133.9, 117.8, 117.0, 82.1, 74.6, 71.6, 70.7, 66.4, 58.5, 33.9, 31.7, 28.4, 25.7, 23.8, 23.7, 23.6, 22.9, 19.5.

Aldehyde (**2-40**)

To oxallyl chloride (0.288 mL, 1.68 mmol) in methylene chloride (3.7 mL) was added dimethyl sulfoxide (DMSO) (0.47 mL, 3.35 mmol) in methylene chloride (0.56 mL) dropwise so that temperature did not exceed -60°C. Alcohol **2-39** (256 mg, 1.52 mmol) in methylene chloride (1.4 mL) was added via addition funnel again not letting temperature exceed -60°C. Reaction mixture was allowed to stir for 15 min and triethyl amine (2.12 mL, 7.62 mmol) was added slowly at -60°C. After allowing flask to warm to room temperature, reaction mixture was poured into water (4.2 mL) and diethyl ether (12 mL). Organic layer was washed with brine (5 mL), dried over sodium sulfate, concentrated and purified by column chromatography to yield aldehyde **2-40** (76% based on recovered starting material): ^{1}H NMR ($CDCl_3$) δ 9.6 (d, J = 8 Hz, 1 H), 6.0 (m, 1 H), 5.2 (m, 2 H), 4.65 (m, 1 H), 4.0 (m, 2 H), 2.4 (m, 1 H), 2.2 (m, 3 H), 2.05 (m, 1 H), 1.8 (q, J = 8 Hz), 1.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 201.5, 134.6, 116.7, 81.2, 70.4, 33.4, 32.9, 31.7, 29.7, 24.8.

Bicyclic Tetrahydrofuran (**2-41**)

To a 0.1M solution of aldehyde **2-40** (88 mg, 0.527 mmol) in benzene (5.2 mL) was added tributyltin hydride (0.16 mL, 0.58 mmol) and AIBN (17.3 mg, 0.105 mmol). The degassed

solution was refluxed for 12 h. At this juncture, only one half of the starting aldehyde had been consumed (by TLC), therefore, an additional amount of tributyltin hydride and AIBN was added (0.16 mL and 17.3 mg, respectively). Following 12 h reflux, reaction mixture was concentrated and purified by flash chromatography to yield furan **2-41** (0.027 g; 31%): ^{1}H NMR ($CDCl_3$) δ 4.5 and 3.9 (t, J = 7.5 Hz, 2 H), 3.7 (m, 2 H), 3.1 (t, J = 9 Hz, 1 H), 2.15 (q, J = 7 Hz, 1 H), 2.0-1.2 (m, 9 H), 1.05 (d, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 85.3, 75.3, 62.5, 53.8, 39.6, 35.6, 33.2, 28.9, 27.8, 16.9; High-resolution MS (EI): Calcd, 170.1307; found, 170.1319.

Anal. Calcd. for $C_{10}H_{18}O_2$: C,70.53; H, 10.66. Found: C, 70.62; H, 10.74.

2-(hydroxyphenylmethyl)cyclohexanone (**3-16**)

Cyclohexenone (0.3 mL, 3.10 mmol), tributyltin hydride (0.92 mL, 3.41 mmol), and AIBN (102 mg, 0.62 mmol) were dissolved in benzene (6.2 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^{0}C and benzaldehyde (0.47 mL, 4.65 mmol) was added. The reaction was allowed to stir for 12 h, concentrated, and diluted with diethyl ether (12 mL). DBU (0.51 mL, 3.41 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the

iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure aldol product **3-16** (0.46 g; 73%) as a mixture of 2 diastereomers (6/1 erythro/threo: ^{1}H NMR ($CDCl_3$) δ 7.2-7.4 (m, 5 H), 5.4 (apparent t, J= 3 Hz ,1 H(erythro)), 4.9 (d of d, J = 2, 8 Hz, 1 H(threo)), 3.0 (s, OH), 2.6-2.3 (m, 3 H), 2.0 (m, 1 H), 1.9-1.6 (complex m, 5 H); ^{13}C NMR ($CDCl_3$) δ 211.0, 136.8, 128.4, 128.2, 127.0, 125.8, 70.7, 57.2, 42.7, 27.9, 26.1, 24.9.[45]

2-(cyclohexylhydroxymethyl)cyclohexanone (**3-17**)

Cyclohexenone (0.4 mL, 4.14 mmol), tributyltin hydride (1.22 mL, 4.55 mmol), and AIBN (136 mg, 0.828 mmol) were dissolved in benzene (8.3 mL) and degassed for 20 m with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^{0}C and cyclohehane-carboxaldehyde (1.0 mL, 8.28 mmol) was added. The reaction was allowed to run for 12 h, concentrated and diluted with diethyl ether (12 mL). DBU (0.74 mL, 4.97 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and

subjected to flash column chromatography (ether/hexanes) to afford the pure aldol product **3-17** (0.49 g; 56%) as a mixture of 2 diastereomers (6/1 erythro/threo: R_f = 0.56 (35% THF/hexane); IR (neat) 3534, 2926, 2853, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (d of d, J = 2, 9 Hz, 1 H(threo)), 3.48 (d of d, J = 3, 7 Hz, 1 H(erythro)), 3.2 (broad s, OH), 2.5-2.0 (m, 3 H), 2.0 (m, 2 H) ,1.9-1.1 (m, 1 H), 1.8-1.0 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 216.0, 75.8, 52.9, 43.0, 39.7, 30.9, 30.4, 27.9, 26.6, 26.3, 25.1; mass spectrum (LSIMS) 211 (M+1, 29.8), 193 (100.0), 95 (93.6), 81 (71.7).

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.22; H, 10.83.

2-(1-hydroxyheptyl)cyclohexanone (**3-18**)

Cyclohexenone (0.5 mL, 5.17 mmol), tributyltin hydride (1.53 mL, 5.69 mmol), and AIBN (170 mg, 1.03 mmol) were dissolved in benzene (11 mL) and degassed for 20 m with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^0C and heptanal (1.44 mL, 10.34 mmol) was added. The reaction was allowed to run for 12 h, concentrated and diluted with diethyl ether (15 mL) . DBU (0.85 mL, 6.2 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced

pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure aldol product **3-18** (0.61 g; 56%) as a mixture of 2 diastereomers: R_f = 0.47 (35% THF/hexane); IR (neat) 3474, 2930, 2858, 1699 cm^{-1} ; ^1H NMR ($CDCl^3$) 4.1 (broad s, OH), 3.7 (apparent t, J = 8 Hz, 1 H), 2.4-2.2 (m, 2 H), 2.1 (m, 1 H), 2.0-1.4 (complex m, 16 H), 0.9 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.0, 71.6, 56.0, 42.9, 33.7, 31.9, 29.4, 27.8, 26.8, 25.0, 22.6, 16.6, 14.0; mass spectrum (CI, methane) 213 (M+1, 19.8), 195 (100.0), 98 (86.5), 81 (39.1), 55 (40.1).

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.52; H, 11.40. Found: C, 73.27; H, 11.33.

2-(hydroxyphenylmethyl)cyclopentanone (**3-19**)

Cyclopentenone (0.34 mL, 4.1 mmol), tributyltin hydride (1.2 mL, 4.51 mmol), and AIBN (133 mg, 0.82 mmol) were dissolved in benzene (8.1 mL) and degassed for 20 m with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^0C and benzaldehyde (0.82 mL, 8.2 mmol) was added. The reaction was allowed to run for 12 h, concentrated, and diluted with diethyl ether (12 mL). DBU (0.73 mL, 4.9 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was

concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure aldol product **3-19** (0.80 g; 79%) as a mixture of 2 diastereomers: R_f = 0.46 (35% THF/hexane); IR (neat) 3445, 3062, 3029, 2966, 2880, 1732 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5 H), 5.25 (apparent t, J = 3 Hz, 1 H), 3.15 (broad s, OH), 2.4-1.4 (complex m, 7 H); ^{13}C NMR ($CDCl_3$) δ 220.4, 143.2, 128.3, 127.9, 127.2, 126.6, 125.6, 71.4, 56.2, 39.2, 22.7, 20.5; mass spectrum (LSIMS) 191 (M+1, 4.5), 173 (100.0), 91 (22.8).

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 75.76; H, 7.42. Found: C, 75.67; H, 7.51.

2-(cyclohexylhydroxymethyl)cyclopentanone (**3-20**)

Cyclopentenone (0.5 mL, 5.97 mmol), tributyltin hydride (1.77 mL, 6.57 mmol), and AIBN (200 mg, 1.19 mmol) were dissolved in benzene (12 mL) and degassed for 20m with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^0C and cyclohehane-carboxaldehyde (1.44 mL, 11.9 mmol) was added. The reaction was allowed to run for 12 h, concentrated and diluted with diethyl ether (15 mL). DBU (1.07 mL, 7.2 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was

concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure aldol product **3-20** (0.72 g; 62%) as a mixture of 2 diastereomers: mp 80-81 ^{o}C; R_f = 0.54 (35% THF/hexane); IR (nujol) 3499, 2923, 2854, 1714 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 4.0 (broad s, OH), 3.55(d, J = 8 Hz, 1 H), 2.5-1.1 (complex m, 18 H); ^{13}C NMR ($CDCl_3$) δ 224.1, 76.1, 51.3, 41.1, 38.5, 30.1, 26.6, 26.4, 25.5, 20.6; mass spectrum (CI, methane) 197 (M+1, 42.4), 179 (100.0), 161 (25.3).

Anal. Calcd. for $C_{12}H_{20}O_2$: C,73.41; H, 10.28. Found: C, 73.05; H, 10.37.

2-(1-hydroxyheptylmethyl)cyclopentanone (**3-21**)

Cyclopentenone (0.5 mL, 5.97 mmol), tributyltin hydride (1.77 mL, 6.57 mmol), and AIBN (200 mg, 1.19 mmol) were dissolved in benzene (12 mL) and degassed for 20 min. with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^{0}C and heptanal (1.66 mL, 11.9 mmol) was added. The reaction was allowed to run for 12h, concentrated and diluted with diethyl ether (15 mL). DBU (1.07 mL, 7.2 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography

(ether/hexanes) to afford the pure aldol product **3-21** (0.75 g; 63%) as a mixture of 2 diastereomers: R_f = 0.48 (35% THF/hexane); IR (neat) 3446, 2957, 2928, 2857, 1733 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 4.2 (s,OH), 4.1 (m, 1 H), 2.4-1.2 (complex m, 18 H), 0.9 (t, J = 3, 7 Hz); ^{13}C NMR ($CDCl_3$) δ 208.0, 69.7, 54.4, 39.1, 34.9, 31.8, 29.2, 26.0, 23.0, 22.6, 20.6, 14.0; mass spectrum (CI, methane) 199 (M+1, 39.2), 181 (100.0), 163 (53.8), 84 (70.5).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.51; H, 11.37.

4-(hydroxyphenylmethyl)-3-hexanone (**3-22**)

4-Hexen-3-one (0.3 mL, 2.63 mmol), tributyltin hydride (0.78 mL, 2.89 mmol), and AIBN (86 mg, 0.525 mmol) were dissolved in benzene (5.3 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^0C and benzaldehyde (0.4 mL, 3.9 mmol) was added. The reaction was allowed to run for 12 h, concentrated and diluted with diethyl ether (10 mL). DBU (0.47 mL, 3.16 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure

aldol product **3-22** (0.28 g; 52%) as a mixture of 2 diastereomers: R_f = 0.54 (35% THF/hexane); IR (neat) 3446, 2966, 2936, 2876, 1705 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 4.8 (d of d, J = 3, 6 Hz, 1H), 2.9 (s, OH), 2.8 (m, 1 H), 2.4-2.0 (m, 2 H), 1.8-1.6 (m 2 H), 1.0- 0.8 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 216.0, 142.0, 128.4, 128.3, 127.8, 127.2, 126.2, 74.2, 60.5, 38.1, 20.7, 12.1, 7.1; mass spectrum (LSIMS) 207 (M+1, 18.6), 189 (46.2), 105 (39.3), 91 (36.3).

Anal. Calcd. for C_{13} $H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.50; H, 9.01.

4-(cyclohexylhydroxymethyl)-3-hexanone (**3-23**)

4-Hexen-3-one (0.5 mL, 4.38 mmol), tributyltin hydride (1.3 mL, 4.82 mmol), and AIBN (144 mg, 0.88 mmol) were dissolved in benzene (9 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^0C and cyclohehane-carboxaldehyde (1.1 mL, 8.76 mmol) was added. The reaction was allowed to run for 12 h, concentrated and diluted with diethyl ether (15 mL). DBU (0.78 mL, 5.26 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to

afford the pure aldol product **3-23** (0.42 g; 45%) as a mixture of 2 diastereomers: R_f = 0.59 (35% THF/hexane); IR (neat) 3462, 2965, 2827, 2853, 1704 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.45(d of d, J = 4, 7 Hz, 1 H), 2.9 (broad s, OH), 2.7 (m, 1 H), 2.5 (m, 2 H), 1.8-1.5 (m, 7 H), 1.4-1.0 (m, 9 H), 0.9 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 216.0, 75.6, 54.9, 40.8, 37.1, 29.6, 28.5, 26.3, 26.1, 25.9, 19.2, 12.3, 7.4; mass spectrum (CI, methane) 213 (M+1, 41), 195 (43.2), 183 (50.6), 129 (81.1), 100 (100.0).

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.52; H, 11.40. Found: C, 73.44; H, 11.37.

2-(phenylmethylidene)cyclohexanone (**3-24**)

Aldol product **3-16** (523 mg, 2.57 mmol) was dissolved in benzene (15 mL) and a catalytic amount of *p*-toluenesulfonic acid (7.3 mg, 0.039 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-24** (0.44 g; 92%) as an oil: E/Z = 82/1 (GC); IR (neat) 2926, 2854, 1674, 1600, 1460 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.25-7.1 (m, 6 H), 3.95-3.85 (m, 2 H), 2.5 (t, J = 7 Hz, 2 H), 1.9 (m, 2 H), 1.75 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 193.3, 136.8, 135.6, 130.4, 130.3, 128.5, 128.4, 40.3, 28.9, 23.9, 23.4.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.60; H, 7.57.

2-(cyclohexylmethylidene)cyclohexanone (**3-25**)

Aldol product **3-17** (142 mg, 0.676 mmol) was dissolved in benzene (2 mL) and a catalytic amount of *p*-toluenesulfonic acid (1.9 mg, 0.01 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-25** (0.12 g; 95%) as an oil: R_f = 0.65 (35% THF/hexane); E/Z = 20/1 (GC); IR (neat) 2926, 2851, 1688, 1615 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 6.43 (d, J = 10 Hz, 1 H), 2.5 (m, 4 H), 2.2 (m, 1 H), 1.8-1.5 (m, 9 H), 1.4-1.1 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 201.2, 144.0, 134.5, 40.1, 36.7, 31.8, 26.6, 25.9, 25.6, 23.7, 23.3; mass spectrum (LSIMS) 193 (M+1, 100.0), 147 (9.0), 111 (90.0).

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.05; H, 10.67.

2-heptylidenecyclohexanone (**3-26**)

Aldol product **3-18** (104 mg, 0.491 mmol) was dissolved in benzene (3 mL) and a catalytic amount of *p*-toluenesulfonic acid (1.4 mg, 0.007 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30

min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-26** (0.085 g; 89%) as an oil: R_f = 0.67 (35% THF/hexane); E/Z = 13/1 (GC); IR (neat) 2951, 2928, 2857, 1687, 1614 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 6.6 (m, 1 H), 2.4 (m, 2 H), 2.05 (q, J = 8 Hz, 2 H), 1.8-1.2 (complex m, 14 H), 0.9 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.3, 139.7, 136.2, 40.1, 31.7, 29.1, 28.5, 27.8, 26.7, 23.6, 23.5, 22.6, 14.0; mass spectrum (EI) 194 (M^+, 60.3), 137 (100.0), 125 (82.0), 111 (80.5), 98 (72.8).

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.34; H,11.42. Found: C, 80.13; H, 11.37.

2-(phenylmethylidene)cyclopentanone (**3-27**)

Aldol product **3-19** (325 mg, 1.7 mmol) was dissolved in benzene (9 mL) and a catalytic amount of *p*-toluenesulfonic acid (2.8 mg, 0.015 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-27** (0.228 g; 78%) as an oil: R_f = 0.53 (35% THF/hexane); E/Z = 15/1 (GC); IR (neat) 3062, 3029, 2940, 2865, 1678, 1592 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.6-7.25 (m, 6 H), 3.0 (m, 2 H), 2.4 (t, J = 8 Hz, 2 H), 2.0 (t, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 200.0,

136.1, 132.3, 130.7, 130.5, 129.3, 128.7, 37.8, 29.3, 20.2; mass spectrum (FAB) 173 (M+1, 100.0), 107 (12.8), 91 (17.6).

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 83.95; H, 6.83.

2-(cyclohexylmethylidene)cyclopentanone (**3-28**)

Aldol product **3-20** (271 mg, 1.38 mmol) was dissolved in benzene (4 mL) and a catalytic amount of *p*-toluenesulfonic acid (4.0 mg, 0.021 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-28** (0.22 g; 90%) as an oil: R_f = 0.58 (35% THF/hexane); E/Z > 100/1 (GC); IR (neat) 2925, 2851, 1721, 1650 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 6.4 (d, J = 10 Hz, 1 H), 2.6 (t, J = 7 Hz, 2 H), 2.4 (m, 2 H), 2.15 (m, 1 H), 1.9 (m, 2 H), 1.8-1.6 (m, 5 H), 1.4-1.1 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ no vis carbonyl, 140.8, 135.3, 38.8, 38.5, 31.7, 26.6, 25.9, 25.5, 19.9; mass spectrum (EI) 178 (M^+, 83.8), 97 (100.0), 79 (34.2).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.84; H,10.18. Found: C, 80.77; H, 10.14.

2-heptylidenecyclopentanone (**3-29**)

Aldol product **3-21** (430 mg, 2.17 mmol) was dissolved in benzene (11 mL) and a catalytic amount of *p*-toluenesulfonic

acid (6 mg, 0.03 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, threw in a dip, and subjected to flash column chromatography to provide eliminated product **3-29** (0.365 g; 94%) as an oil: R_f = 0.60 (35% THF/hexane); E/Z = 41/1 (GC); IR (neat) 2956, 2928, 2857, 1719, 1649 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 6.5 (m, 1 H) 2.6 (m, 2 H), 2.25 (t, J = 8 Hz, 2 H), 2.15 (m, 2 H), 1.95 (m, 2 H), 1.4-1.2 (m, 8 H), 0.9 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.8, 137.2, 136.2, 38.5, 31.6, 29.6, 29.0, 28.3, 26.7, 22.5, 19.8, 13.9; mass spectrum (EI) 180 (M^+, 37.3), 123 (100.0), 97 (90.4).

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.93; H, 11.19. Found: C, 79.55; H, 11.21.

1-phenyl-2-ethyl-1-pentene-3-one (**3-30**)

Aldol product **3-22** (134 mg, 0.648 mmol) was dissolved in benzene (2 mL) and a catalytic amount of *p*-toluenesulfonic acid (1.8 mg, 0.01 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-30** (0.64 g; 53%) as an oil: R_f = 0.60 (35% THF/hexane); E/Z =

23/1 (GC); IR(neat) 2976, 2936, 2875, 1660 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.4 (m, 6 H), 2.9 (m, 2 H), 2.5 (m, 2 H), 1.2-1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 192.0, 137.5, 134.3, 129.7, 128.9, 128.5, 31.0, 19.9, 13.7, 8.8; mass spectrum (EI) 188 (M^+, 33.2), 159 (64.2), 131 (100.0), 91 (71.8).

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.07; H, 8.75.

1-cyclohexyl-2-ethyl-1-penten-3-one (**3-31**)

Aldol product **3-23** (140 mg, 0.66 mmol) was dissolved in benzene (5 mL) and a catalytic amount of *p*-toluenesulfonic acid (1.8 mg, 0.01 mmol) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 30 min. The crude mixture was diluted with ether, washed twice with aq. sat. sodium bicarbonate, dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to provide eliminated product **3-31** (0.112 g; 88%) as an oil: R_f = 0.72 (35% THF/hexane); E/Z = 34/1 (GC); IR (neat) 2980, 2930, 2865, 1668, 1630 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 6.35 (d, J = 10 Hz, 1 H), 2.65 (q, J = 7 Hz, 2 H), 2.3 (q, J = 8 Hz, 2 H), 1.8-1.0 (m, 14 H), 0.95 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.7, 146.8, 141.1, 38.0, 32.4, 30.7, 30.5, 25.7, 19.2, 14.8, 8.9; mass spectrum (EI) 194 (M^+, 13.9), 179 (18.0), 165 (100.0), 81 (35.6).

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.34; H, 11.42. Found: C, 80.03; H, 11.48.

2-heptyl-2-(hydroxyphenylmethyl)cyclopentanone (**3-32**)

Compound **3-29** (287 mg, 1.59 mmol), tributyltin hydride (0.47 mL, 1.75 mmol), and AIBN (52 mg, 0.319 mmol) were dissolved in benzene (4 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to 10^0C and benzaldehyde (0.39 mL, 3.19 mmol) was added. The reaction was allowed to run for 12 h, concentrated and diluted with diethyl ether (10 mL). DBU (0.29 mL, 1.94 mmol), and 2-3 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure aldol product **3-32** (0.16 g); recovered 0.11 g starting material, 59% yield with respect to reacted starting material: R_f = 0.53 (35% THF/hexane); ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5 H), 4.8 (s, 1 H), 3.2 (s, OH), 2.3-1.2 (complex m, 18 H), 0.9 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ no vis carbonyl, 140.0, 127.9, 127.7, 127.4, 76.7, 56.5, 39.6, 32.7, 32.6, 31.8, 30.5, 30.4, 29.1, 24.7, 22.6, 19.1, 14.1.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.11; H, 9.79. Found: C, 79.05; H, 9.76.

2-allylcyclohexanone (**3-40**)

Cyclohexenone (0.35 mL, 3.62 mmol), tributyltin hydride (1.07 mL, 3.98 mmol), and AIBN (119 mg, 0.724 mmol) were dissolved in benzene (3.6 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (3.15 mL, 18.1 mmol) was added; the reaction mixture was stirred for 2-3 min. Allyl bromide (1.25 mL, 14.5 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.59 mL, 3.98 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-40** (0.30 g; 60%): R_f = 0.64 (35% THF/hexane); ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.0 (m, 2 H), 2.5 (m, 1 H), 1.65 (m, 2 H), 2.4-1.8 (complex m, 8 H); ^{13}C NMR ($CDCl_3$) δ 212.5, 136.5, 116.2, 50.3, 42.0, 33.8, 33.4, 27.9, 25.0.[67]

2-benzylcyclohexanone (**3-41**)

Cyclohexenone (0.35 mL, 3.62 mmol), tributyltin hydride (1.07 mL, 3.98 mmol), and AIBN (119 mg, 0.724 mmol) were dissolved in benzene (3.6 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (3.15 mL, 18.1 mmol) was added; the reaction mixture was stirred for 2-3 min. Benzyl bromide (1.72 mL, 14.5 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.59 mL, 3.98 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-41** (0.47 g; 69%): R_f = 0.60 (35% THF/hexane); ^{1}H NMR ($CDCl_3$) δ 7.3-7.1 (m, 5 H), 3.3-3.1 (d of d, J = 5,14 Hz, 1 H), 2.6-2.2 (complex m, 4 H), 2.0 (m, 2 H), 1.8-1.4 (complex m, 4H); ^{13}C NMR ($CDCl_3$) δ 212.5, 140.4, 129.2, 128.3, 126.0, 52.5, 42.2, 35.5, 33.5, 228.1, 25.1; mass spectrum CI (methane) 189 (M+1,100.0), 171 (10.4), 119 (3.9).[68]

2-hexylcyclohexanone (3-42)

Cyclohexenone (0.35 mL, 3.62 mmol), tributyltin hydride (1.07 mL, 3.9 mmol), and AIBN (119 mg, 0.724 mmol) were dissolved in benzene (3.6 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (3.15 mL, 18.1 mmol) was added; the reaction mixture was stirred for 2-3 min. Iodohexane (2.14 mL, 14.5 mmol) was added, and the reaction was allowed to reflux for 14h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.59 mL, 3.98 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-42** (0.40 g; 61%): R_f = 0.68 (35% THF/hexane); ^{1}H NMR ($CDCl_3$) δ 2.4-2.2 (m, 3 H), 2.2-2.0 (m, 2 H), 1.9-1.6 (m, 4 H), 1.4-1.2 (m, 10 H), 0.9 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.0, 50.8, 41.9, 33.8, 31.8, 29.4 (high intensity; probably 2 coincidental C's), 28.0, 27.2, 24.8, 22.6, 14.1.[69]

4-ethylhept-6-en-3-one (**3-43**)

4-Hexen-3-one (0.33 mL, 2.89 mmol), tributyltin hydride (0.85 mL, 3.18 mmol), and AIBN (95 mg, 0.578 mmol) were dissolved in benzene (2.9 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (2.5 mL, 14.5 mmol) was added; the reaction mixture was stirred for 2-3 min. Allyl bromide (1.0 mL, 11.6 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.47 mL, 3.18 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-43** (0.194 g; 48%): R_f = 0.70 (35% THF/hexane); IR (neat) 3079, 2966, 2937, 1713; ^{1}H NMR ($CDCl_3$) δ 5.75-5.6 (m, 1 H), 5.0 (m, 2 H), 2.5-2.1 (complex m, 5 H), 1.7-1.4 (m, 2 H), 1.1-1.0 (t, J = 7 Hz, 3 H), 0.9-0.8 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.0, 135.9, 116.5, 53.2, 35.8, 35.6, 24.4, 11.7, 7.5; mass spectrum (CI,methane) 141 (m+1, 100), 140 (55.4), 112 (18.5), 111 (43.5), 83 (88.0).

Anal. Calcd. for $C_9H_{16}O$: C, 77.08; H, 11.51. Found: C, 77.31; H, 11.76.

4-benzyl-3-hexanone (**3-44**)

4-Hexen-3-one (0.33 mL, 2.89 mmol), tributyltin hydride (0.85 mL, 3.18 mmol), and AIBN (95 mg, 0.578 mmol) were dissolved in benzene (2.9 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (2.5 mL, 14.5 mmol) was added; the reaction mixture was stirred for 2-3 min. Benzyl bromide (1.37 mL, 11.6 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.47 mL, 3.18 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-44** (0.22 g; 40%): R_f = 0.68 (35% THF/hexane); ^1H NMR ($CDCl_3$) δ 7.3-7.1 (m, 5 H), 2.9-2.6 (m, 3 H), 2.4-2.0 (m, 2 H), 1.7-1.4 (m, 2 H), 0.9 (2t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 211.5, 139.9, 128.6, 127.7, 126.2, 55.4, 38.0, 36.9, 25.0, 11.8, 7.4.

3-ethyl-1-phenyl-1,4-hexanedione (**3-45**)

4-Hexen-3-one (0.30 mL, 2.63 mmol), tributyltin hydride (0.78 mL, 2.89 mmol), and AIBN (87 mg, 0.53 mmol) were dissolved in benzene (2.7 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (2.3 mL, 13.2 mmol) was added; the reaction mixture was stirred for 2-3 min. Bromoacetophenone (1.57 g, 7.89 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.47 mL, 3.18 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-45** (0.28 g; 62%): ^{1}H NMR ($CDCl_3$) δ 8.0 (m, 2 H), 7.4 (m, 3 H), 3.5 (m, 1 H), 3.2 (m, 1 H), 3.0 (d of d, J = 17.7, 3.9 Hz, 1 H) 2.6 (m, 2 H), 1.6 (m, 2 H), 1.1 (t, J = 7.2 Hz, 3 H), 0.9 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.2, 200.0, 133.1, 129.0, 128.6, 128.1, 47.5, 40.1, 36.0, 24.9, 11.7, 7.7.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.02; H, 8.32. Found: C, 76.90; H, 8.27.

methyl 3-ethyl-4-oxohexanoate (**3-46**)

4-Hexen-3-one (0.30 mL, 2.63 mmol), tributyltin hydride (0.78 mL, 2.89 mmol), and AIBN (87 mg, 0.53 mmol) were dissolved in benzene (2.7 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (2.3 mL, 13.2 mmol) was added; the reaction mixture was stirred for 2-3 min. Methyl bromoacetate (0.73 mL, 7.89 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.47 mL, 3.18 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-46** (0.36 g; 80%): ^{1}H NMR ($CDCl_3$) δ 3.6 (s, 3 H), 2.9 (m, 1 H), 2.7 (d of d, J = 10.5, 9.9 Hz, 1 H) 2.5 (q, J = 7.2 Hz, 2 H), 2.3 (d of d, J = 13.8, 4.5, 1H), 1.6 (m, 2 H), 1.0 (t, J = 7.5 Hz, 3 H), 0.9 (t, J =

7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.3, 172.9, 51.4, 48.0, 35.4, 34.5, 24.4, 11.1, 7.4.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.75; H, 9.37. Found: C, 62.61; H, 9.31.

allylbicyclic ketone (**3-47**)

Unsaturated ketone **3-39**[70] (0.30 mL, 1.85 mmol), tributyltin hydride (0.55 mL, 2.04 mmol), and AIBN (60.7 mg, 0.37 mmol) were dissolved in benzene (1.6 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (1.6 mL, 9.25 mmol) was added; the reaction mixture was stirred for 2-3 min. Allyl bromide (0.64 mL, 7.4 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.31 mL, 2.08 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-47** (0.291 g; 76%): R_f = 0.71 (35% THF/hexane); IR (neat) 3074, 2926, 2862, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8-5.6 (m, 1 H), 5.0 (m, 2 H), 2.6-2.2 (m, 5

H), 1.9-1.0 (complex m, 11 H), 1.3 (minor), 1.07(major) (s, 3 H); mass spectrum (CI,methane) 207 (M+1, 100), 149 (14.22), 110 (30.4), 109 (89.6), 96 (26.1).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.63; H, 10.83.

Benzylbicyclic ketone (**3-48**)

Unsaturated ketone **3-39**[70] (0.30 mL, 1.85 mmol), tributyltin hydride (0.55 mL, 2.04 mmol), and AIBN (60.7 mg, 0.37 mmol) were dissolved in benzene (1.6 mL) and degassed for 20 min with a steady stream of argon. The reaction mixture was refluxed 4 h until starting material had been consumed (monitored by TLC). The reaction vessel was cooled to room temperature and HMPA (1.6 mL, 9.25 mmol) was added; the reaction mixture was stirred for 2-3 min. Benzyl bromide (0.88 mL, 7.4 mmol) was added, and the reaction was allowed to reflux for 14 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.31 mL, 2.08 mmol) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure alkylated product **3-48** (0.31 g; 65%): R_f = 0.66 (35% THF/hexane); IR (neat) 3026, 2926, 2862, 1710, 743,

700 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.3-7.1 (m, 5 H), 3.1-2.2 (complex m, 5 H), 1.8-1.0 (complex m, 11 H), 1.2,1.05 (s, 3 H); mass spectrum CI (methane) 257 (M+1, 93.7), 239 (60.6), 91 (3.6).

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.31; H, 9.44. Found: C, 84.04; H, 9.33.

methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**3-52**)

To D-ribose (12.5 g, 0.083 mol) in acetone (47.5 mL) and methanol (47.5 mL) was added concentrated hydrochloric acid (1.25 mL). The reaction mixture was allowed to reflux overnight. After cooling and neutralization with pyridine, the mixture was poured into water (100 mL) and extracted with diethyl ether (170 mL). Following a wash with saturated sodium sulfate, the organic layer was dried and concentrated under reduced pressure to afford **3-52** (7.04 g; 41%). (The compound was used crude in the subsequent reaction.): ^1H NMR ($CDCl_3$) δ 5.0 (d J = 1.2, 1 H), 4.8 (broad d, J = 5.4, 1 H), 4.6 (broad d, J = 6, 1 H), 4.4 (apparent s, 1 H), 3.6 (m, 2 H), 3.4 (s, 3 H), 3.3 (broad s, OH), 1.5 (s, 3 H), 1.3 (s, 3 H).[51]

Iodinated protected D-ribose (**3-49**)

Compound **3-52** (2.0 g, 0.0098 mol) was dissolved in acetonitrile (20 mL) at room temperature. The following reagents were added in sequence: triphenylphosphine (6.16 g, 23.53 mmol), imidazole (2.0 g, 29.4 mmol), and iodine (5.98 g, 23.52 mmol). Following a 15 h reflux period, the mixture

was diluted to 3X volume with hexanes; the subsequently formed triphenylphosphine precipitate was removed by filtration. The crude mixture was then subjected to flash chromatography to afford pure **3-49** (2.68 g; 87%): ^{1}H NMR ($CDCl_3$) δ 5.0 (s, 1 H), 4.7 (d, J = 5.7 Hz, 1 H), 4.6 (d, J = 6 Hz, 1 H), 4.4 (m, 1 H), 3.4 (s, 3 H), 3.2 (m, 2 H), 1.5 (s, 3 H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 112.6, 109.7, 87.4, 85.4, 83.1, 55.2, 26.5, 25.1, 6.7; High-resolution MS (M + 1): calcd, 315.0015; found, 315.0103.

Anal. Calcd. for $C_9H_{15}O_4I$: C, 34.39; H, 4.81. Found: C, 34.30; H, 4.76.

1,2:3,4-O-isopropylidene-D-galactopyranose (**3-54**)

Acetone (640 mL) and concentrated sulfuric acid (6.4 mL) were stirred together while adding D-galactose (8 g, 0.61 mmol) slowly. Following a stirring period of 20 h, the reaction pot was cooled in an ice bath while ammonia gas was bubbled through the mixture until a pH of 7 was reached. The resulting ammonium sulfate precipitate was filtered and the filtrate was concentrated under reduced pressure and used crude in the subsequent reaction. ^{1}H NMR ($CDCl_3$) δ 5.5 (d J = 5.4 Hz, 1 H), 4.6 (d of d, J = 7.8, 2.4 Hz, 1 H), 4.35 (q, J = 2.4 Hz, 1 H), 4.25 (d of d, J = 8.1, 1.8 Hz, 1 H), 3.8 (complex m, 3 H), 2.8 (broad s, OH), 1.5 (s, 3 H), 1.4 (s, 3 H), 1.3 (s, 6 H).[52]

Iodinated protected D-galactose (**3-50**)

Compound **3-54** (2.0 g, 0.0077 mol) was dissolved in acetonitrile (15.4 mL) at room temperature. The following reagents were added in sequence: triphenylphosphine (4.85 g, 18.5 mmol), imidazole (1.57 g, 23.1 mmol), and iodine (4.7 g, 18.5 mmol). Following a 15 h reflux period, the mixture was diluted to 3X volume with hexanes; the subsequently formed triphenylphosphine precipitate was removed by filtration. The crude mixture was then subjected to flash chromatography to afford pure **3-50** (2.3 g; 81%): ^{1}H NMR ($CDCl_3$) δ 5.5 (d of d, J = 5.0, 1.5 Hz, 1 H), 4.6 (d of q, J = 7.8, 1.5 Hz, 1 H), 4.4 (d of d, J = 7.8, 1.8 Hz, 1 H), 4.3 (m, 1 H), 3.9 (t, J = 7.2 Hz, 1 H), 3.3 (m, 2 H), 1.5 (s, 3 H), 1.4 (s, 3H), 1.32 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 109.5, 108.8, 96.7, 71.6, 71.2, 70.7, 69.0, 26.4, 26.0, 24.9, 24.5, 2.2; High-resolution MS (M + 1): calcd, 371.0277; found, 371.0335.

Anal. Calcd. for $C_{12}H_{19}O_5I$: C, 38.92; H, 5.17. Found: C, 38.98; H, 5.11.

2-(3-oxocyclohexyl)cyclohexanone (**3-60**)

2-Cyclohexenone (0.35 mL, 3.6 mmol), tributyltin hydride (1.1 mL, 4.0 mmol) and AIBN (119 mg, 0.7 mmol) were dissolved in benzene (3.6 mL). The solution was degassed for 20 m. with a steady stream of argon. The reaction mixture was then refluxed until starting material was consumed by TLC (*ca.* 4 h.). The reaction vessel was cooled to room temperature and

HMPA (3.2 mL, 18.1 mmol) was added; the reaction mixture was stirred for 2-3 m. Then, 2-cyclohexenone (0.42 mL, 4.3 mmol) was dissolved in benzene (8.6 mL) and added via addition funnel (approx. 10 drops/min); the reaction was allowed to reflux for 14-18 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.6 mL) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure conjugate addition product **3-60** (0.29 g; 41%): ^{1}H NMR ($CDCl_3$) δ 2.5-2.2 (complex m,5 H), 2.1-2.0 (m, 2 H), 1.95-1.4 (complex m, 11 H). High-resolution MS (M+1): Calcd, 195.1307; Found, 195.1259.

2-(3-oxobutyl)cyclohexanone (**3-61**)

2-Cyclohexenone (0.35 mL, 3.6 mmol), tributyltin hydride (1.1 mL, 4.0 mmol) and AIBN (119 mg, 0.7 mmol) were dissolved in benzene (3.6 mL). The solution was degassed for 20 m. with a steady stream of argon. The reaction mixture was then refluxed until starting material was consumed by TLC (*ca.* 4 h.). The reaction vessel was cooled to room temperature and HMPA (3.2 mL, 18.1 mmol) was added; the reaction mixture was stirred for 2-3 m. Then, methyl vinyl ketone (0.33 mL, 4.0

mmol) was dissolved in benzene (8 mL) and added via addition funnel (approx. 10 drops/min); the reaction was allowed to reflux for 14-18 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.6 mL) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure conjugate addition product **3-61** (0.19 g; 31%): IR(neat) 2926, 2857, 1708, 1449, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ2.6-2.2 (complex m, 5 H), 2.1 (s,3 H), 2.0-1.8 (complex m, 4 H), 1.7-1.3 (complex m,4 H); ^{13}C NMR ($CDCl_3$) δ212.8, 208.6, 49.8, 42.1, 41.3, 34.3, 29.8, 28.0, 25.0, 23.8.[71]

8-methylnonyl 3-(2-oxocyclohexyl)propanoate (**3-62**)

2-Cyclohexenone (0.35 mL, 3.6 mmol), tributyltin hydride (1.1 mL, 4.0 mmol) and AIBN (119 mg, 0.7 mmol) were dissolved in benzene (3.6 mL). The solution was degassed for 20 m. with a steady stream of argon. The reaction mixture was then refluxed until starting material was consumed by TLC (*ca.* 4 h.). The reaction vessel was cooled to room temperature and HMPA (3.2 mL, 18.1 mmol) was added; the reaction mixture was stirred for 2-3 m. Then, isodecyl acrylate (0.96 mL, 4.0 mmol) was dissolved in benzene (8 mL) and added via addition

funnel (approx. 10 drops/min); the reaction was allowed to reflux for 14-18 h. The reaction mixture was then cooled to room temperature, diluted to 3X volume with diethyl ether, and washed 4X with brine. To the organic layer was added DBU (0.6 mL) and 2-3 drops of water; an ethereal solution of iodine was added dropwise to the stirring solution until the iodine color persisted, and the solution was rapidly filtered through silica gel with ether. Finally, the filtrate was concentrated under reduced pressure and subjected to flash column chromatography (ether/hexanes) to afford the pure conjugate addition product **3-62** (0.43 g; 38%): ^{1}H NMR ($CDCl_3$) δ 4.0 (q, J = 7 Hz, 2 H), 2.4-2.2 (m, 3 H), 2.1-2.0 (m, 2 H), 1.8-1.0 (complex m, 17 H), 0.9-0.7 (m, 10 H).

Anal. Calcd. for $C_{19}H_{36}O_3$: C, 73.49; H, 11.04. Found: C, 73.27: H, 10.89.

ethyl α-hydroxymethylacrylate (**4-6**)

Triethyl phosphonoacetate (44.8 g, 0.2 mol) and a 37% aqueous solution of formaldehyde (68 mL) was stirred vigorously at room temperature. A saturated solution of potassium carbonate (48 g, 0.35 mol) was slowly added (30 min) to the reaction flask while reaction temperature was maintained under 40°C. Stirring was continued for 1 h. Then a saturated ammonium chloride solution (75 mL) was added and, the mixture was extracted with diethyl ether (3 X 30 mL). Following drying the combined organic layers with magnesium sulfate, the solvent was removed under reduced pressure. The

crude material was distilled (70°C/5 mm Hg) to afford **4-6** (19.5 g; 75%): ^{1}H NMR ($CDCl_3$) δ 6.2 (s, 1 H), 5.8 (s, 1 H), 4.3 (d, J = 6.3 Hz, 2 H), 4.2 (q, J = 7.2 Hz, 2 H), 3.1 (s, OH), 1.3 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.3, 139.8, 125.2, 62.0, 60.8, 14.1.[55]

ethyl α-bromomethlyacrylate (**4-7**)

Phosphorus (III) bromide (5.4 mL, 0.57 mmol) was added to a stirring solution containing α-hydroxymethylacrylate (16.2 g, .124 mol) in freshly distilled diethyl ether (118 mL) at -10°C. The reaction was stirred for 3 h during which the temperature was allowed to rise to 20°C. Following cooling the reaction flask to -10°C, water (70 mL) was added and the solution extracted with hexanes (3 X 25 mL). The organic layer was washed with saturated sodium chloride (2 X 25 mL) and then dried with magnesium sulfate. The solvent was removed under reduced pressure and the residual oil was distilled (78-80°C/14 mmHg) to afford **4-7** (17 g; 71%): ^{1}H NMR ($CDCl_3$) δ 6.3 (s, 1 H), 6.0 (s, 1 H), 4.3 (q, J = 7.2 Hz, 2 H), 4.2 (s, 2 H), 1.3 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.3, 137.6, 128.9, 61.3, 29.4, 14.2.[55]

ethyl α-benzenesulfinylmethylacrylate (**4-8**)

To ethyl α-bromomethyl acrylate (2.1 g, 0.0107 mol) in methanol (11 mL) was slowly added benzenesulfinic acid, sodium salt (3.5 g, 0.022 mol). Following a reflux period of 6 h, the reaction was quenched with water and extracted with

diethyl ether. The organic layer was dried with sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography to afford **4-8** (2.2 g; 80%): R_f = 0.36 (35% THF-hexanes); ^{1}H NMR ($CDCl_3$) δ 7.8-7.5 (m, 5 H), 6.5 (s, 1 H), 5.9 (s, 1H), 4.2 (s, 2H), 4.0 (q, J = 7.2 Hz, 2H), 1.2 (t, J = 7.2 Hz, 3 H).[54]

ethyl α-tributylstannylmethylacrylate (**4-9**)

Compound **4-8** (1.8 g, 7.1 mmol), tributyltin hydride (3.8 mL, 14.2 mmol), and AIBN (47 mg, 0.28 mmol) were dissolved in benzene (60 mL) and refluxed for 1.5 h. The solution was concentrated and distilled under full pump (118°-128°C/3 mm Hg) to afford **4-9** (1.7 g; 61%): ^{1}H NMR ($CDCl_3$) δ 6.0 (s, 1 H), 5.2 (s, 1 H), 4.0 (q, J = 7.2 Hz, 2 H), 2.1 (t, J = 30 Hz, 2 H), 1.6 (m, 6 H), 1.4 (m, 6 H), 0.9 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 167.8, 142.0, 118.3, 60.6, 29.4, 27.8, 15.6, 14.3, 14.0, 10.2.[54]

ethyl 2-((3-oxocyclohexyl)methyl)propenoate (**4-11**)

A solution consisting of 2-cyclohexenone (0.16 mL, 1.7 mmol), the 2-substituted allyl stannane **4-9** (1.3 g, 0.0033 mol), and AIBN (54 mg, 0.33 mmol) in benzene (0.8 mL) was degassed and refluxed for 18 h. Following concentration under reduced pressure the crude material was subjected to flash chromatography to afford **4-11** (0.21 g; 61%): R_f = 0.51 (35% THF-hexanes); ^{1}H NMR ($CDCl_3$) δ 6.2 (s, 1 H), 5.5 (s, 1 H), 4.1 (q, J = 7.2 Hz, 2 H), 2.4-2.1 (complex m, 5 H), 2.0-

1.5 (complex m, 4 H), 1.7-1.3 (complex m, 2 H), 1.3 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.4, 167.0, 138.2, 126.6, 60.8, 47.6, 41.4, 39.0, 37.9, 31.1, 25.0, 14.2; High-resolution MS (M+1): Calcd, 210.1256; Found, 210.1297.

ethyl 2-((3-oxocyclopentyl)methyl)propenoate (**4-12**)

A solution consisting of 2-cyclopentenone (0.16 mL, 1.9 mmol), the 2-substituted allyl stannane **4-9** (1.2 g, 0.003 mol), and AIBN (62 mg, 0.38 mmol) in benzene (0.9 mL) was degassed and refluxed for 18 h. Following concentration under reduced pressure the crude material was subjected to flash chromatography to afford **4-12** (0.22 g; 58%): R_f = 0.49 (35% THF-hexanes); ^1H NMR ($CDCl_3$) δ 6.2 (s, 1 H), 5.5 (s, 1 H), 4.2 (q, J = 7.2 Hz, 2 H), 2.4-2.0 (complex m, 7 H), 1.8-1.5 (complex m, 2 H), 1.2 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 219.1, 167.0, 138.9, 126.1, 60.8, 44.8, 38.3, 37.7, 36.0, 29.1, 14.2; High-resolution MS (M+1): Calcd, 196.1099; Found, 196.1113.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22. Found: C, 67.22: H, 8.11.

ethyl 2-(2-methyl-4-oxohexyl)propenoate (**4-13**)

A solution consisting of 4-hexen-3-one (0.15 mL, 1.3 mmol), the 2-substituted allyl stannane **4-9** (850 mg, 2.1 mmol), and AIBN (43 mg, 0.26 mmol) in benzene (1.3 mL) was degassed and refluxed for 18 h. Following concentration under reduced pressure the crude material was subjected to

flash chromatography to afford **4-13** (0.18 g; 65%): R_f = 0.63 (35% THF-hexanes); ^{1}H NMR ($CDCl_3$) δ 6.1 (s, 1 H), 5.4 (s, 1 H), 4.1 (q, J = 7.2 Hz, 2 H), 2.4-2.1 (complex m, 7 H), 1.2 (t, J = 7.2 Hz, 3 H), 1.0 (t, J = 7.2 Hz, 3 H), 0.81 (d, J = 5.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.1, 167.2, 139.1, 126.2, 60.7, 49.2, 39.1, 36.3, 28.8, 19.7, 14.2, 7.7; High-resolution MS (EI): Calcd, 212.1412; Found, 212.1369.

Hexa-(-)-menthylditin (**5-13**)

To a flame-dried 250 mL 3-neck flask was added magnesium powder (4.1 g, 0.170 mol), THF (37 mL), and ethyl bromide (0.55 mL). Then, (-)-menthyl chloride[72] (23 g, 0.131 mol) in THF (43 mL) was added via addition funnel over a period of 3.5 h at 50° C followed by reflux for 30 min. The reaction mixture was then cooled to below room temperature and slowly added via cannula to tin tetrachloride (2.8 mL, 24 mmol) in benzene (26 mL) at 0° C followed by reflux for 30 min. This method was successful in transferring the prepared Grignard reagent without transferring the inorganic salts that had formed in the bottom of the Grignard flask. After the addition, the reaction was heated to reflux for 4 h and then left stirring at room temperature for 12 h. The reaction was then quenched with 10% aqueous hydrochloric acid (5.5 mL) and extracted with diethyl ether (120 mL). The organic layer was washed 2X with ammonium chloride (sat.aq.), 3X with H_2O, and then dried over sodium sulfate. Following concentration under reduced pressure, the white paste was recrystallized

from ethanol yielding **5-13** (5.5 g; 43%) as a fine white powder: mp > 220° C; $[\alpha]_D^{20}$ -212° (c = 1; C_6H_6); ^1H NMR ($CDCl_3$) δ 2.3-0.7 series of multiple signals from which clearly emerge three doublets, 0.80 (d, J = 6.6 Hz), 0.86 (d, J = 5.7 Hz), 0.91 (d, J = 6.6 Hz).[65]

tri-(-)menthyltin bromide (**5-14**)

Hexa-(-)-menthylditin (**5-13**) (5.1 g, 0.0048 mol) was stirred in carbon tetrachloride (30 mL) at 0° C while bromine (0.27 mL, 5.2 mmol) was added dropwise. The reaction flask was wrapped in aluminum foil to exclude light during the bromine addition as well as the 12 h stirring period necessary to complete the reaction. Following concentration under reduced pressure, the resulting dark residue was recrystallized from ethanol 3X to afford **5-14** (3.6 g; 61%): mp 143-145 °C; $[\alpha]_D^{20}$ -78° (c = 1, C_6H_6). ^1H NMR ($CDCl_3$) δ 2.15 (m, 3 H), 1.95 (m, 3 H), 1.7 (m, 6 H), 1.5 (m, 6 H), 1.3 (m, 6 H), 1.0 (m, 6 H), 0.96 (d, J = 6.6 Hz, 9 H), 0.87 (d, J = 5.7 Hz, 9 H), 0.82 (d, J = 6.6 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 46.5, 43.6, 41.0, 35.4, 35.3, 35.0, 27.1, 22.6, 22.1, 16.9.[65]

tri-(-)-menthyltin hydride (**5-15**)

A solution of tri-(-)-menthytin bromide **5-14** (2.0 g, 0.0033 mol) in THF (19 mL) was added dropwise to a suspension of lithium aluminum hydride powder (130 mg, 3.4 mmol) in THF (6 mL). The reaction was stirred at room temperature for 3

h. Then the reaction flask was cooled to 0°C and quenched slowly with a solution containing H_2O (0.25 mL) in dioxane (0.89 mL). Following filtration to remove any inorganic salts, the filtrate was dried over sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography (using hexane only) to afford pure **5-15** (1.5 g; 84%) as a transparent, extremely sticky oil: $[\alpha]_D^{20}$ -56.5 (c = 1.6, C_6D_6); ^1H NMR (C_6D_6) δ 5.4 (s, Sn-H), 2.1 (d of d, J = 12.6, 2.4, 3 H), 1.9 (m, 3 H), 1.75 (m, 9 H), 1.5 (m, 6 H), 1.25 (m, 3 H), 1.0-0.6 (m, 6 H), 1.0 (d, J = 6.6, 9 H), 0.90 (d, J = 2.4, 9 H), 0.88 (d, J = 3.0, 9 H); ^{13}C NMR (C_6D_6) δ 47.7, 43.2, 36.0, 35.8, 34.4, 33.8, 27.2, 22.9, 22.3, 16.3; High-resolution MS (M + 1): Calcd, 539.3561; found, 539.3498.

(-)-menthyltrimethyltin (**5-18**)

To a flame-dried 3-neck flask was added magnesium powder (3.2 g, 0.130 mol), THF (30.4 mL), and ethyl bromide (0.45 mL). Then, (-)-menthyl chloride[72] (18.8 g, 0.107 mol) in THF (34.4 mL) was added via addition funnel over a period of 3 h at 50°C followed by reflux for 30 min. Next, trimethyltin chloride (9.3 g, 0.047 mol) in diethyl ether (43 mL) was added via addition funnel at 0°C over a period of 4 h. Following an additional stirring period of 48 h at room temperature, the reaction flask was cooled to 0°C, quenched slowly with H_2O (0.4 mL), and allowed to stir for 1 h. The crude material was filtered, concentrated under reduced

pressure, and purified by flash chromatography to afford **5-18** (12.2 g; 85%) as a colorless liquid: $[\alpha]_D^{20}$ -33° (c = 2.1, benzene); ^{1}H NMR ($CDCl_3$) δ 1.9-1.5 (complex m, 4 H), 1.3 (m, 3 H), 1.0 (m, 3 H), 0.95 (d, J = 8 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H), 0.75 (d, J = 7 Hz, 3 H), 0.05 (t, J = 25 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 46.6, 40.7, 35.6, 35.2, 33.2, 31.6, 26.5, 22.6, 22.1, 15.5, -10.5.[64]

(-)-menthyldimethyltin bromide (**5-19**)

A vigorously stirred emulsion of (-)menthyltrimethyltin (2.0 g, 0.0066 mol) in methanol (24 mL) was treated dropwise with bromine (0.33 mL, 6.4 mmol) at 0°C excluding all light. Following a stirring period of 12 h, the solution was concentrated to afford crude **5-19** (2.5 g; quant.): ^{1}H NMR ($CDCl_3$) δ 2.4-2.0 (complex broad m, 1 H), 1.7 (complex m, 4 H), 1.5 (complex m, 1 H), 1.4-1.2 (complex m, 4 H), 0.9 (complex m, 12 H), 0.7 (t, J = 25 Hz, 3 H); ^{13}C NMR (C_6D_6) δ 46.0, 39.7, 39.0, 35.2, 35.0, 33.8, 26.5, 22.5, 22.1, 15.4, -1.8, -2.1.[64]

(-)menthyldimethyltin hydride (**5-20**)

A solution of (-)-menthyldimethyltin bromide **5-19** (1.2 g, 0.0033 mol) in diethyl ether (9.3 mL) was added dropwise to a suspension of lithium aluminum hydride (120 mg, 3.3 mmol) in diethyl ether (6 mL) at room temperature. The reaction was allowed to stir overnight. Then, the reaction was quenched slowly with hydrated sodium sulfate and filtered

to remove the inorganic salts. The solvent was evaporated under reduced pressure, and the crude product was purified by Khugelrhor distillation to afford **5-20** (0.85 g; 90%): $[\alpha]_D^{20}$ -37.1 (c = 1.3, C_6D_6); ^1H NMR (C_6D_6) δ 5.23 (s, Sn-H), 2.4-2.0 (complex m, 1 H), 1.8-0.8 (series of complex multiplets, 21 H), 0.6 (t, J = 25 Hz, 3 H); High-resolution MS (EI): Calcd, 290.1056; found, 290.0978.

dimethyldi-(-)-menthyltin (**5-22**)

To a flame-dried 3-neck flask was added magnesium powder (320 mg, 13.2 mmol), THF (3.2 mL), and 2 drops ethyl bromide. Then, (-)-menthyl chloride[72] (1.8 g, 0.0102 mol) in THF (3.8 mL) was added via addition funnel over a period of 2.5 h at 50°C followed by reflux for 30 min. Next, (-)-menthyldimethyltin bromide, **5-19** (1.5 g, 0.0041 mol) in diethyl ether (4.8 mL) was added via addition funnel at room temperature over a period of 2 h. Following stirring overnight, the reaction flask was cooled to 0°C, quenched slowly with H_2O (0.13 mL), and allowed to stir for 1 h. The crude material was filtered, concentrated under reduced pressure, and purified by flash chromatography to afford **5-22** (1.7 g; 95%): ^1H NMR ($CDCl_3$) δ 1.82-0.94 (complex m, 20 H), 0.92 (d, J = 6.9 Hz, 6 H), 0.84 (d, J = 6.6 Hz, 6 H), 0.72 (d, J = 6.6 Hz, 6 H), -0.9 (t, J = 23 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 46.6, 41.3, 35.6, 35.3, 33.6, 32.9, 26.7, 22.7, 22.2, 15.9, -11.5; High-resolution MS (EI): Calcd, 428.2465; found, 428.2439.[63]

methyldi-(-)-menthyltin bromide (**5-23**)

A vigorously stirred emulsion of dimethyl-(-)-dimenthyltin, **5-22** (1.5 g, 0.0034 mol) in 12.4 mL methanol was treated dropwise with bromine (0.17 mL, 0.0033 mol) at 0°C excluding all light. Following a stirring period of 12 h, the solution was concentrated to afford crude **5-23** (1.6 g; quant.): ^{1}H NMR ($CDCl_3$) δ 2.2-1.2 (m, 20 H), 1.1-0.7 (complex m, 18 H), 0.55 (t, J = 21.5 Hz, 3 H).[63]

methyl di-(-)-menthyltin hydride (**5-24**)

A solution of methyl di-(-)-menthyltin bromide **5-23** (1.7 g, 0.0034 mol) in diethyl ether (9.7 mL) was added dropwise to a suspension of lithium aluminum hydride (140 mg, 3.6 mmol) in diethyl ether (6.2 mL) at room temperature. The reaction was allowed to stir overnight. Then, the reaction was slowly quenched with hydrated sodium sulfate and filtered to remove the inorganic salts. The solvent was evaporated under reduced pressure, and the crude product was purified by Khugelrhor distillation of afford **5-24** (0.94 g; 68%): $[\alpha]_D^{20}$ -50.2 (c = 1.6, C_6D_6); ^{1}H NMR (C_6D_6) δ 5.1 (s, Sn-H), 2.4-1.2 (complex m, 20 H), 0.94 (d, J = 6.9 Hz, 6 H), 0.88 (d, J = 5.1 Hz, 6 H), 0.85 (d, J = 6.3 Hz, 3 H), 0.80 (d, J = 6.9 Hz, 3 H), -0.6 (t, J = 23 Hz, 3 H).[63]

methyldineophyl-(-)-menthyltin (**5-26**)

A vigorously stirred emulsion of (-)-menthyltrimethyltin **5-18** (12.1 g, 0.040 mol) in methanol (145 mL) was treated dropwise with bromine (4 mL, 77.7 mmol) at 0°C excluding all light. Following a stirring period of 12 h, the solution was concentrated to afford the intermediate product (-)-menthylmethyltin dibromide **5-25** as a dark orange oil. In a separate flame-dried 250 mL round bottom flask was added magnesium powder (2.8 g, 0.117 mol), THF (25 mL), and ethyl bromide (0.37 mL). Then, neophyl chloride in THF (30 mL) was added via addition funnel over a period of 3.5 h at room temperature, followed by 45 min reflux. The reaction mixture was cooled to below room temperature and slowly added via cannula to (-)-menthylmethyltin dibromide synthesized above (8.0 g, 0.019 mol) in benzene (19 mL). Then, the reaction was heated to reflux for 4 h. After cooling to room temperature, the reaction was quenched with 10% hydrochloric acid, filtered, concentrated under reduced pressure, and purified by flash chromatography to afford **5-26** (9.2 g; 92%). ^{1}H NMR ($CDCl_3$) δ 7.4-7.1 (m, 10 H), 1.7-0.9 (complex m, 26 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.76 (d, J = 6.3 Hz, 3 H), 0.64 (d, J = 6.6 Hz, 3 H), -0.38 (t, J = 24.3 Hz, 3 H).[62]

dineophyl-(-)-menthyltin bromide (**5-27**)

A vigorously stirred emulsion of methyldineophyl-(-)-menthyltin **5-26** (8.2 g, 0.015 mol) in methanol (45 mL) was

treated dropwise with bromine (0.78 mL, 15.1 mmol) at 0°C excluding all light. Following a stirring period of 6 h, the solution was concentrated to afford crude **5-27** (9.1 g; quant.): ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 10 H), 1.7-1.4 (m, 9 H), 1.4 (s, 12 H), 1.34 (s, 4 H), 1.3-1.0 (m, 1 H), 0.90 (d, J = 5.4 Hz, 3 H), 0.72 (d, J = 4.2 Hz, 3 H), 0.70 (d, J = 5.7 Hz, 3 H).[62]

dineophyl-(-)-menthyltin hydride (**5-28**)

A solution of dineophyl-(-)-menthyltin bromide, **5-27** (8.5 g, 0.014 mol) in THF (55 mL) was added dropwise to a suspension of lithium aluminum hydride (560 mg, 14.7 mmol) in THF (25 mL) at room temperature. The reaction was allowed to stir for 4 h. Then, the reaction was slowly quenched with a solution consisting of H_2O (1.1 mL) in dioxane (3.9 mL) and filtered to remove inorganic salts. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography to afford **5-28** (6.7 g; 91%): $[\alpha]_D^{20}$ -28.7° (c = 1.5, benzene); ^{1}H NMR (C_6D_6) δ 7.3-7.1 (m, 10 H), 4.9 (s, Sn-H), 1.7-1.4 (m, 6 H), 1.39 (s, 2 H), 1.34 (s, 12 H), 1.32 (s, 2 H), 1.2-1.0 (m, 4 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.68 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.3, 128.4, 127.9, 125.8, 46.4, 41.8, 37.6, 35.8, 35.4, 33.3, 32.5, 31.7, 29.8, 29.2, 26.7, 22.8, 22.1, 15.7; High resolution MS (m + 1): Calcd, 527.2622; found, 527.2658.

Anal. Calcd. for $C_{30}H_{46}Sn$: C, 68.58; H, 8.82. Found: C, 68.67: H, 8.83.[62]

General Procedures for the asymmetric reduction of acetophenone

Method A: Acetophenone (1 eq.), AIBN (0.2 eq.), and the desired chiral tin compound **5-15, 5-20,** or **5-24** (1.2 eq.) were dissolved in benzene (1 M), degassed with argon, and allowed to reflux until no acetophenone was present (by TLC). The mixture was diluted to 3X volume with diethyl ether. Then HCl (5% aq. sat., 1-2 mL) was added and the mixture was stirred for 2-4 min. The solution was washed with brine, dried over sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography to afford pure pinacol product **5-17** or pure 1-phenylethanol **5-21**.

Method B: Acetophenone (0.18 mL, 1.5 mmol), AIBN (50 mg, 0.3 mmol), and the desired chiral tin compound **5-28**, or **5-15** (3.0 mmol) was added to a Pyrex test tube and irradiated with a Hanovia 450W medium pressure Hg-vapor lamp using a cooling apparatus (see Figure 5-2) for 24 h. The mixture was diluted to 3X volume with diethyl ether. Then HCl (5% aq. sat., 1-2 mL) was added and the mixture was stirred for 2-4 min. The solution was washed with brine, dried over sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography to afford pure pinacol product **5-17** or pure 1-phenylethanol **5-21**.

Pinacol product (**5-17**)

Produced by reaction with **5-15** using both **method A** and **method B** (undetermined yield): R_f = 0.43 (20% THF/hexane); ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 10 H), 2.6 and 2.35 (s, OH), 1.6 and 1.5 (s, 6 H). There are two OH and two methyl peaks because both possible pinacol products formed in a ratio of 1:1.

(-)-(S)-1-phenylethanol (**5-21**)

R_f = 0.43 (20% THF/hexane); ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5 H), 4.8 (q, J = 6.3 Hz, 1 H), 2.5 (broad s, OH), 1.4 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.9, 128.5, 127.5, 125.4, 70.4, 25.2.

Produced by reaction with **5-20** using **method A**: (82% yield); $[\alpha]_D^{20}$ -1.43° (c = 5, ethanol).

Produced by reaction with **5-24** using **method A**: (70% yield); $[\alpha]_D^{20}$ -3.62° (c = 5, ethanol).

Produced by reaction with **5-28** using **method B**: (40% yield); $[\alpha]_D^{20}$ -2.7° (c = 5, ethanol).

LIST OF REFERENCES

1. Geise, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: New York, 1986.

2. Pine, S.H. *Organic Chemistry*; McGraw-Hill: New York, 1987.

3. Motherwell, W.B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: New York, 1992.

4. (a) Gomberg, M. *J. Am. Chem. Soc.* **1990**, *22*, 757; (b) Gomberg, M. *Chem. Ber.* **1990**, *33*, 3150.

5. Hey, D.H.; Waters, W.A. *Chem. Rev.* **1937**, *21*, 169.

6. Kharasch, M.S.; Margolis, E.T.; Mayo, F.R. *J. Org. Chem.* **1937**, *2*, 393.

7. (a) Mayo, F.R.; Lewis, F.M. *J. Am. Chem. Soc.* **1944**, *66*, 1594; (b) Mayo, F.R.; Lewis, F.M. *Discuss. Faraday Soc.* **1947**, *2*, 285.

8. (a) Burnett, J.F. *Acc. Chem. Res.* **1978**, *11*, 413; (b) Minisci, F. *Top. Curr. Chem.* **1976**, *622*, 1.

9. (a) Hart, D.J. *Science* **1984**, *233*, 883; (b) Geise, B. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553; (c) Curran, D.P. *Synthesis* **1988**, 417; 489; (d) Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448; (e) Neumann, W.P. *Synthesis* **1987**, *8*, 665.

10. Menapace, L.W.; Kuivila, H.G. *J. Am. Chem. Soc.* **1964**, *86*, 3047.

11. Pereyre, M.; Quintard, J.P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.

12. van der Kerk, G.J.M.; Noltes, J.G.; Luitjen, J.G.A. *J. Appl. Chem.* **1957**, *7*, 356.

13. (a) Coates, D.A.; Tedder, J.M. *J. Chem. Soc., Perkin Trans 2* **1973**, 1570; (b) Tanner, D.D.; Diaz, G.E.; Potter, A. *J. Org. Chem.* **1985**, *50*, 2149.

14. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: London, 1976.

15. (a) Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* **1982**, *104*, 5829; (b) Keck, G.E.; Enholm, E.J.; Yates, J.B.; Wiley, M.R. *Tetrahedron* **1985**, *41*, 4079.

16. Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* **1985**, *41*, 3925.

17. Baldwin, J.E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

18. (a) Beckwith, A.L.J.; Phillipou, G; Serelis, A.K. *Tetrahedron Lett.* **1981**, *22*, 2811; (b) Beckwith, A.L.J.; Meijs, G.F. *J. Chem. Soc., Perkin Trans 2* **1979**, 1535.

19. Curran, D.P.; Geise, B.; Porter, N.A. *Stereochemistry of Free Radical Reactions*; VCH: New York, 1996.

20. Houk, K.N.; Spellmeyer, D.C. *J. Org. Chem.* **1987**, *52*, 959.

21. (a) Pereyre, M.; Godet, J. *Tetrahedron Lett.* **1970**, 3653; (b) Pereyre, M.; Godet, J. *J.Organometallic Chem.* **1972**, *40*, C23.

22. Beckwith, A.L.J.; Roberts, D.H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.

23. Sugarwara, T.; Otter, B.A.; Veda, T. *Tetrahedron Lett.* **1988**, *29*, 75.

24. Enholm, E.J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939.

25. Enholm, E.J.; Burroff, J.A. *Tetrahedron Lett.* **1992**, *33*, 1835.

26. House, H.O. *Modern Synthetic Reactions*; Benjamin/ Cummings: London, 1972.

27. Enholm, E.J.; Kinter K.S. *J. Am. Chem. Soc.* **1991**, *113*, 7784.

28. Enholm, E.J.; Xie, Y.P.; Abboud, K. *J. Org. Chem.* **1995**, *60*, 1112.

29. Enholm, E.J.; Whitley, P.E. *Tetrahedron Lett.* **1995**, 9157.

30. Enholm, E.J.; Whitley, P.E. *Tetrahedron Lett.* **1996**, 559.

31. Enholm, E.J.; Whitley, P.E.; Xie, Y.P. *J. Org. Chem.* **1996**, *61*, 5384.

32. March, J. *Advanced Organic Chemistry*; Wiley-Interscience: New York, 1992.

33. Hudlicky, T.; Koszyk, K.F. *J. Org. Chem.* **1980**, *45*, 5020.

34. (a) Enholm, E.J.; Jia, Z.J. *Tetrahedron Lett.* **1995**, *36*, 6819; (b) Enholm, E.J.; Jia, Z.J. *Tetrahedron Lett.* **1996**, *37*, 1177.

35. Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry Part B*; Plenum Press: New York, 1990.

36. Luche, J. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

37. Corey, E.J.; Meyers, A.G. *Tetrahedron Lett.* **1984**, *25*, 3559.

38. Blankey, C.J.; Sauter, F.J. *Organic Synthesis, Coll. Vol. V*; John Wiley: New York, 1973; pp 258-263.

39. (a) Charles, R.G. *J. Org. Chem.* **1957**, *22*, 677; (b) Sacconi, L.; Ciampolini, M. *J. Chem. Soc.* **1964**, 276.

40. Davies, A.G.; Smith, P.J. *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, 1982; Vol.2, p 519.

41. Shibata, I; Baba, A. *Org. Prep. Proced. Int.* **1994**, *26*, 87.

42. Trost, B.M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591.

43. Kuwajima, I; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.

44. Pereyre, M.; Valade, J. *J. Organometal. Chem.* **1968**, *11*, 97.

45. House, H.O.; Crumrine, D.S. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

46. Yamamoto, Y; Yataga, H. *J. Chem. Soc., Chem. Commun.* **1981**, 162.

47. Stille, J.K.; Shenvi, S. *Tetrahedron Lett.* **1982**, 627.

48. Curran, D.P.; Chang, C. *J. Org. Chem.* **1989**, *54*, 3140.

49. Kinter, K.S. Ph.D. Thesis, University of Florida, May 1993.

50. Pereyre, M.; Odic, Y. *J. Organometal. Chem.* **1973**, *55*, 3140.

51. Barrett, A.G.; Lebold, S. *J. Org. Chem.* **1990**, *55*, 3853.

52. Ballou, C.F.; Fischer, H.D. *J. Am. Chem. Soc.* **1954**, *76*, 3188.

53. (a) Enholm, E.J.; Trivellas, A. *Tetrahedron Lett.* **1994**, 1627; (b) Takai, K.; Nitta, K.; Fujimura, O; Utimoto, K. *J. Org. Chem.* **1989**, *54*, 4732; (c) Curran, D.P.; Fevig, T.L.; Totleben, M.J. *Synlett* **1990**, 733; (d) Molander, G.A.; Harring, L.S. *J. Org. Chem.* **1990**, *55*, 6171; (e) Molander, G.A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439; (f) Curran, D.P.; Fevig, T.L.; Jasperse, C.P.; Totleben, M.J. *Synlett* **1992**, 943; (g) Totleben, M.J.; Curran, D.P.; Wipf, P. *J. Org. Chem.* **1992**, *57*, 1740; (h) Curran, D.P.; Totleben, M.J. *J. Am. Chem. Soc.* **1992**, *114*, 6050; (i) Molander, G.A.; McKie, J.A. *J. Org. Chem.* **1992**, *57*, 3132.

54. Baldwin, J.E.; Adlington, R.M., Lowe, C.; O'Neil, I.A; Sanders, G.L. *J. Chem. Soc., Chem. Commun.* **1988**, 1030.

55. Villieras, J.; Ramband, M. *Synthesis*, **1982**, 924.

56. Dhar, R.K. *Aldrichimica Acta.* **1994**, *27*, 43.

57. Morrison, J.D. *Asymmetric Synthesis*, Vol 1-5; Academic Press: New York, 1983-1985.

58. (a) Midland, M.M. *Chem. Rev.* **1989**, *89*, 1553; (b) Brown, H.C.; Park, W.S.; Cho, B.T. *J. Org. Chem.* **1987**, *52*, 5406; (c) Brown, H.C.; Ramachandran, P.V. *Acc. Chem. Res.* **1992**, *25*, 16.

59. Noyori, R. *Chemtech* **1992**, 360.

60. Porter, N.A.; Scott, D.M.; McPhail, A.T. *Tetrahedron Lett.* **1990**, *31*, 1679.

61. (a) Renaud, P.; Schubert, S. *Angew. Chem. Int. Ed. Eng.* **1990**, *29*, 433; (b) Renaud, P.; Schubert, S. *Synlett* **1990**, 624.

62. Podesta, J.C.; Chopa, A.B.; Vitale, C.A. *J. Organomet. Chem.* **1995**, *494*, 11.

63. Podesta, J.C.; Vitale, C.A. *J. Chem. Soc., Perkin Trans 1* **1996**, 2407.

64. Schumann, H.; Wasserman, B.C.; Hahn, E. *Organometallics* **1992**, *11*, 2803.

65. Podesta, J.C.; Radivoy, G.E. *Organometallics* **1994**, *13*, 3364.

66. Hopps, H.B.; Backer, H.J. *Aldrichim. Acta* **1970**, *3*(4),9.

67. Tsuda, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421.

68. Guindon, Y.; Yoakim, C. *J. Org. Chem.* **1984**, *49*, 3912.

69. Suzuki, A.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 275.

70. Heathcock, C.H.; Ellis, J.E.; McMurray, J.E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.

71. Rathke, M.W.; Olsen, R.S. *Synth. Commun.* **1986**, *16*, 1133.

72. Smith, J.G.; Wright, G.F. *J. Org. Chem.* **1952**, *17*, 1116.

BIOGRAPHICAL SKETCH

Paul Whitley was born in Russellville, Kentucky, a small rural town located in the south-central section of the state. He was the "baby" of the family, being the last of Jean and Carey Whitley's four children. His mom taught him reading and basic math before he was old enough to go to school, which seemed to set the tone for Paul being ahead of most of his classmates for all of his academic career. Besides the normal childhood activities of climbing trees, riding bikes, and playing sports, Paul spent countless hours playing with Lego building blocks and taking apart every electronic item he could get his hands on. His first chemical reactions were mixing his dad's toiletry items with various household products, much to his parents' dismay.

His education, kindergarten through high school, was carried out in the Russellville Independent school system. Most classes seemed easy for him, but Paul still found the educational experience challenging and interesting. There were many extra-curricular activities in which he participated such as the Gifted and Talented Program and Science Club. Paul always excelled in science and knew that he wanted to spend his life doing something related to the sciences.

Paul attended college at Western Kentucky University in Bowling Green, Kentucky. After majoring in civil engineering, mechanical engineering, and pre-pharmacy, Paul settled on chemistry as his major of choice. Organic chemistry seemed to interest him the most. He performed undergraduate research for Dr. Tom Green who was studying the various different types of sulfur functionalities in coal and petroleum.

Paul received an excellent opportunity when he was hired for two summers as a co-op student at Logan Aluminum, a factory in his hometown. He worked in the chemistry lab and was able to observe how the "industrial world" works. It was at this point where Paul observed the types of work a B.S. chemist does compared to a Ph.D. chemist. These observations combined with the encouragement from his college professors convinced Paul to attend graduate school.

He chose Dr. Eric Enholm, who was at the University of Florida, to further his educational career. He soon discovered that graduate school was much more intellectually stimulating and challenging than anything he had previously encountered. The professors at the UF Dept. of Chemistry, especially his research advisor, pushed him to excel and learn much about the field of synthetic organic chemistry.

Though he realizes that there is still an enormous amount to be learned, his graduate career is over; he now finds himself on the verge of another gigantic step. He is ready and eager to step out into the industrial world where

he can hopefully apply the experience and knowledge which he has spent his whole life acquiring.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eric J. Enholm, Chair
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier Jr.
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

David H. Powell
Associate Scientist of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Charles M. Allen Jr.
Professor of Biochemistry and Molecular Biology

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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